# PATHOLOGY OF ATOMIC BOMB CASUALTIES*

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The energies released in atomic explosions embrace the entire range from that of mechanical shock waves to that of gamma rays. The effects on exposed tissues are modified not only by the characteristics of the bomb but by the conditions of exposure. As it happened, the injuries were not qualitatively different in Hiroshima and Nagasaki. The descriptions of the lesions must, however, be regarded as representative only of the changes produced at those two cities. Whether or not the explosion of other bombs, or of like bombs under different conditions, would produce comparable effects cannot be stated.

## METHODS AND MATERIALS

Since the Joint Commission was not able to begin its work in Japan until some 6 weeks after the bombings of August 6, 1945, at Hiroshima and August 9, 1945, at Nagasaki, by which time most of those who were to die from radiation effects had succumbed, it was necessary to secure clinical records and necropsy protocols and specimens from Japanese clinicians and pathologists to supplement materials obtained at necropsy by members of the Joint Commission itself. Some of these pathologists were attached to the Commission in a group of some sixty Japanese physicians who were to aid in the clinical field study. Others had been with "research parties" that had been sent into the stricken cities by various universities and by the Japanese Army Medical Service to conduct medical investigations. To the last mentioned we owe the only available records and materials from the patients dying within the first

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This paper is a summary of a portion of a report to the Surgeons General of the Armed Forces by the "Joint Commission for the Investigation of the Atomic Bomb in Japan." The Commission was comprised of U.S. Army personnel under the direction of Col. Ashley W. Oughterson, M.C., of personnel of the "Manhattan District" under Col. Stafford L. Warren, M.C., and of U.S. Navy personnel under Capt. Shields Warren, M.C., U.S.N.R. After the field study which was designed to obtain as detailed and accurate an estimate as possible of the types and numbers of casualties, of the mechanisms of injury, and of factors in protection, the report was prepared at the Army Institute of Pathology.

few days following the bombing. These were obtained for study through the aid of the Japanese Surgeon General Hiraye. Many of these "research parties" were staffed by the best available Japanese scientists who did work of a high order of excellence. Gradually a list of these pathologists was constructed—no small task since provincialism and professional jealousy were not unknown in the academic circles of Japan. In the work of establishing contact with these men and obtaining the necessary materials, the Joint Commission was greatly aided by Dr. Masao Tsuzuki, then Professor of Surgery at the Tokyo Imperial University, and chief of the medical section of the Japanese National Research Council. It was his influence that unlocked cabinets of material that could otherwise easily have remained sealed. The records were translated word by word from the original protocols by a team comprised of the pathologist who had performed the necropsy, one of the English speaking pathologists attached to the Joint Commission, and one of the American pathologists of the Commission. In many instances it was necessary to travel into remote parts of Japan to obtain the records and materials at first hand from the files of the smaller universities. When gross specimens were still available, they were checked against the descriptions in the protocols. Most of these were found to be quite accurate. Blocks were then taken from the original specimens to check and supplement the usually better fixed tissue in the smaller specimen jars and also the paraffin blocks and finished histologic preparations that were requested in the original letters written by Dr. Tsuzuki. The histologic slides were checked also against the protocols as they were received.

The records and materials were brought back to the United States where additional sections were prepared and illustrations made through the facilities of the Army Institute of Pathology. The Naval Medical Research Institute aided materially in working up the Nagasaki material. The necropsy protocols were transcribed into standard United States Army Medical Department form. Each was assigned a "Key Number," by which it is filed under the general A.I.P. accession number 158930. Reference to patients in the present text is made according to this key as "K" followed by the appropriate numeral.

After a preliminary review, tissues from 170 patients were found sufficiently well preserved to warrant detailed histologic study. For purposes of statistical tabulation, however, only the last 16 necropsies of the Nagasaki series, which had been performed after the 40th day by members of the Joint Commission itself, were found useful, since only in those protocols was there a record of the distance from the point of

explosion, and of possible protective factors. These factors usually were recorded in the Hiroshima protocols since the Japanese pathologists there had been keenly aware of their supreme significance. Moreover, many of the patients had been soldiers within well defined areas of the large military encampment (Chugoku Army Headquarters), one of whose boundaries was almost directly beneath the point of explosion of the bomb. Consequently, the detailed tabulations are based on a total of 110 patients, 94 from Hiroshima and 16 from Nagasaki, although occasional reference is made to the earlier Nagasaki material. It may be unequivocally stated that at least the temporal sequence of anatomic changes in heavily exposed patients in the two cities is similar. Lamentably, an exact comparison by distance from the bomb is not possible on the basis of the material at hand.

The concurrent clinical studies of some 14,000 patients, and the protection and casualty surveys are summarized in the general Medical Report of the Joint Commission.[47]

## The Injurious Factors—General Statement

The physical factors of distance and the condition of the blanket of atmosphere at the moment of explosion are two important determinants of the effects of the bombs. Both bombs were exploded many hundreds of yards above the cities. In the discussion to follow the distances are stated from the point on the ground above which the explosion occurred, not from the explosion itself. The former point is variously referred to as the "hypocenter," "ground center," or "ground zero."

The injurious factors and the damage inflicted are summarized in

Table I

*Energies and Effects of the Atomic Bomb*

| Energy | Injury | Type or target of injury |
|---|---|---|
| I. Mechanical | A. Trauma | 1. Direct (blast)<br>2. Indirect (falling débris) |
| II. Radiant<br>a. Thermal | B. Burns | 1. Direct ("flash burns")<br>2. Indirect |
| b. Ionizing radiations | C. Radiation effect | 1. Skin<br>2. Gastro-intestinal tract<br>3. Gonads<br>4. Lymphoid tissue<br>5. Marrow<br>6. Other tissues |

general terms in Table I. Often the three main types of injury coexisted: traumatic, thermal, and ionizing radiation. For purposes of clarity, these will, however, be discussed separately. Traumatic and thermal injury accounted for the vast majority of the casualties.

*Traumatic Injuries*

In considering the mechanical effects of the explosion, direct blast injury and the indirect effects produced by collapsing buildings and flying débris must be distinguished. As in the bombings of Great Britain, the latter was far more important in producing casualties than the former.

Direct blast injury to ears, lung, and intestines analogous to that inflicted by high explosive bursting within a few feet was almost unknown. At the prevailing distance from the target the explosion did not have the hammer-blow effect of high explosive,[20,98] but rather was like a sudden violent gust of air which lasted for a brief but appreciable period. There was a short, positive phase followed by a longer, but less destructive, negative phase. The relative ineffectiveness of the latter was indicated by the nature of the damage to buildings, most of which showed a preponderance of effects indicating a thrust away from the bomb. At a Hiroshima hospital soon after the bombing only 8 of 371 patients who were examined had ruptured ear drums, although 19 suffered temporary deafness. Seventy-six per cent of this group of men had been within 2000 yds. of the center. In the survivors examined by the Joint Commission after the sixth week, less than 1 per cent, even of those who had been within the first 1000 yds., had ruptured ear drums, and beyond 1500 yds. the incidence fell below 0.1 per cent. Not a single middle ear or tympanum was available for microscopic examination from the patients in whom there was a clinical suggestion of blast injury. The foci of pulmonary emphysema and atelectasis without hemorrhage observed in some of the early casualties (Fig. 20) are difficult to interpret. These were found frequently at death in patients who had not been exposed to blast. Many patients lost consciousness for brief periods, although they could not remember any direct trauma aside from blast. A few were injured by being hurled forcibly, sometimes for considerable distances, against solid objects, but this must be considered an indirect effect of the blast.

Immensely more injury was inflicted by the indirect effect of the blast —the falling débris and masonry. How many were killed outright will never be known accurately. Thousands were pinned beneath the wreckage and were soon consumed by the holocaust of fire that swept the city and which made rescue impossible. In October of 1945, 2 months after the explosion, it was remarkable to note how few were the survivors who had suffered really severe injury. Thus in survivors at Hiroshima the incidence of fractures was less than 4.5 per cent. It was not that injuries

were few; rather, almost none who had lost the capacity to move escaped the flames.

Very characteristic were the lesions inflicted by flying glass (Fig. 1). This material often split into long spear-shaped fragments, even as far as 3 miles from the explosion. The fragments were hurled with such force as to become embedded in the wood of the opposite walls. As was to be expected, the wounds were multiple and often penetrating. Often keloids appeared following injury of this type (as is not infrequent in the Japanese race), and arteriovenous aneurysm sometimes resulted from injuries of the vessels.

Since some of the patients had suffered injury also from ionizing radiations with consequent leukopenia, it is obvious that even minor traumatic wounds might become the seat of infections which could become generalized.

*Burns*

As in the case of the mechanical forces, direct and indirect factors in the causation of the burns must be considered. Direct "flash" burns resulted from exposure to the radiant energy of the bomb. This energy was transmitted in a spectrum resembling that of the sun. In the present section only that band including the ultraviolet, visible light, and infrared rays will be considered. The exact intensities of these various components cannot be stated, but it is probable that all contributed to the damage to the skin of exposed human beings. All of the component rays were transmitted in straight lines at the velocity of light. Consequently, only surfaces directly exposed were burned and intervening objects cast "shadows."

To understand the "flash burns" one must conceive of a very large amount of radiant energy acting for an extremely brief interval of time. The intensity is indicated by the effect on granite which within several hundred yards showed fragmentation of its surface caused by an unequal expansion of its components. It has been estimated that a temperature of at least 2000° C. is necessary to produce this effect. The brevity of the peak intensity of the flash is indicated by the fact that the "shadows" of constantly moving and easily shriveled objects, such as leaves, are sharply outlined on wood behind them—and exposed wood was superficially carbonized even at 3000 yds. from the center.[47]

The rays in their rectilinear course burned whatever profile, including that of man, directly faced the center of the explosion. Thus the burns typically were very sharply outlined. Intervening objects also cast sharp protective shadows on the skin. Those close to the bomb suffered searing

or charring of the skin to the level of the subcutaneous tissue and died shortly (Fig. 3). Death was the fate of more than 95 per cent of those directly exposed to the bomb within 1200 yds. of the point above which the bomb exploded. Beyond this, clothes were some protection. The darker shades absorbed more heat as is demonstrated by selective scorching of the dark polka dots, or stripes, or flowers on a contrasting lighter pattern. Occasionally, such parts of the skin as underlay the darker portions of the pattern were selectively injured (Fig. 2). Sometimes, however, burns occurred beneath unaltered cloth, where it was tightly stretched over the skin in those patients closest to the explosion (Fig. 4).

Between 1500 and 2000 yds. the burns varied in their severity, some showing complete destruction of the derma, others being of second degree. From the data of Ashe and Roberts[5] it is learned that a temperature of 400° C. acting for approximately 0.5 seconds is necessary to produce a second degree burn. The exact numbers of calories absorbed by various surfaces exposed to the bomb are not known, since the duration and intensity curve of the heat flux are matters of conjecture. As 2000 yds. was approached, some cutaneous surfaces ultimately showed, after an initial phase of erythema and blistering, depigmentation with superficial damage or no damage to the epithelium (Fig. 4). Beyond this distance, and up to 4000 yds., the opposite change, an intense pigmentation resembling that of ordinary but extreme sunburn, followed the initial erythema. This deep chocolate colored mask was well shown in a group of men who had been prisoners in the city jail at approximately 2500 yds. from the hypocenter (Fig. 5).

Closer inspection of the sharply outlined "profile" or "flash" burns after healing showed that even the most severely burned areas usually were surrounded by an intensely pigmented zone, and this, in turn, by a narrow band of depigmented tissue whose overlying epithelium was intact (Fig. 8). Even the centrally depigmented but otherwise little damaged skin showed similar phenomena of pigmentation—a broad pigmented area surrounding the central, most-directly exposed zone of depigmentation, with a narrow ring of depigmented tissue again separating the hyperpigmented skin from the surrounding normal tissue.

Practically all of the burns became infected, and many which had been of the second degree ultimately showed deep destruction of tissue as a result of bacterial action. The sharp outlines of the burns often were disturbed, as undermining ulcerations of bacterial causation developed. The infections, as in the case of the mechanical injuries, were particularly

important in those who were within 1500 yds. and who had received a significant dose of radiation.

Occasionally the thermal injury, coupled with infection, resulted in chondritis of the ear, which, in healing, produced a scarred, shrunken, and distorted auricle.

Keloids were observed frequently and were extreme in some patients (Fig. 7) within 10 weeks. Their subsequent development has been described by Block and Tsuzuki.[9] More than three-fourths of the healing second and third degree burns showed some overgrowth of scar tissue. The tentative conclusion of the Japanese observers was that keloids probably were not more frequent than would be expected in this race in ordinary, infected, poorly treated burns. This conclusion has not been altered by subsequent observations of the survivors.[9]

Histologically, there is evidence confirming the gross observation that depigmentation of the skin can occur even if the epithelium of the surface is not completely destroyed (Figs. 6, 11, and 12). In that portion of the skin which had been most severely burned, the epithelium of the surface was necrotic and contained pyknotic nuclear remnants, both of polymorphonuclear cells and large mononuclear phagocytes. Very few leukocytes were present in the adjacent corium and deeper lying perivascular tissue. At the margins of the denuded area the epithelial cells of the malpighian stratum had lost their pigment and no dermal melanophores were found. Some other epithelial cells had become vacuolated and were in disarray. At a still greater distance from the zone of destruction the epithelium was relatively well preserved and its basal layers had become excessively pigmented. There some dermal melanophores also were seen. More laterally still there was a much less pigmented zone but there again was evidence of a more deeply penetrating burn. The zone of hyperpigmentation corresponded to that observed grossly. In this particular case, however, there had occurred also some severe injury more peripherally which precluded complete interpretation of the gross appearance. These observations indicate that complete destruction of epithelium is unnecessary for depigmentation to occur. They suggest also that some special band of the spectrum, probably in the ultraviolet, might be responsible for this phenomenon. The diverse effects upon the skin of different bands in the ultraviolet have been pointed out recently.[12,13] Much is still to be learned concerning the action of high intensities in the ultraviolet range.

The results of infection in the presence of leukopenia were seen in a section from a small burn in a patient who was at 1000 yds. and who received no other serious burns. The epithelium had completely sloughed

(Fig. 13). On the homogeneous, dull pink-staining surface of the collagen were present irregular, granular, purple-staining masses of cocci. Some of these occurred in islets as much as 1 mm. below the surface and one clump actually lay within a bundle of smooth muscle (arrector pili). Squamous metaplasia had occurred in the ducts of the sweat glands. There appeared to have been actual proliferation of these cells, many of which were large and irregular with tremendous vesicular nuclei. The acini of the sweat glands, however, exhibited shrinkage of the epithelium and irregular thickening and compaction of the basement membrane, in some cases with partial collapse of the acinus. Nowhere was there a leukocytic infiltration in the vicinity of the bacterial masses. In one small portion of the surface a very thin layer of squamous epithelial cells remained. These cells were much swollen, some were multinucleated, and in all instances the vesicular nuclei contained very prominent chromatin knots. These changes are ascribed to thermal effect, but what direct rôle ionizing radiations played is difficult to assess. The evidence of indirect effect of the ionizing radiations lies in the total absence of leukocytic response to the injury and to the bacteria that are seen in section.

In another case, the subepithelial tissues contained a scanty exudate consisting largely of monocytes situated within extravasated fibrinous material. One vessel was found to have a necrotic wall and a lumen filled with a thrombus which consisted largely of fibrin (Fig. 14). Deeper in the subcutaneous tissue of the same specimen was a remarkable basophilic ground substance containing irregular large cells with basophilic cytoplasm. Some of these had the granules of mast cells (Fig. 15).

Severe burns caused by contact with flame rarely were observed by the Joint Commission, for the same reason that relatively few severe traumatic injuries were seen among the survivors. The gathering fires spread so rapidly within the cities that only those who were not severely injured could escape. Occasionally, dark clothing burst into flame on those within 1500 yds. of the hypocenter and contact burns resulted. Such burns lacked the sharp outlines produced by shadowing, and the "profile" characteristics seen in the flash burns. Their course also was affected by infection and leukopenia.

## *Radiation Effects*

### Etiologic Factors

During the explosion of the atomic bomb, vast quantities of ionizing radiations were released in the form of gamma rays, neutrons, beta particles, alpha particles, radioactive fission products, and possibly some

of the unexploded radioactive substance of the bomb itself. Factors of distance and shielding are of special importance in considering the effects of these radiations. Thus, the beta and alpha particles can be disregarded since they travel only a short distance through air. The fission products largely were swept into the stratosphere by the violent updraft created by the heat of the explosion. There was no biologic evidence that significant amounts of these materials had been deposited upon the target. Potentially of greater significance may be the neutrons, for they can be projected for considerable distances through the atmosphere. Their effectiveness in damaging tissue is several times greater than that of gamma rays, measured in roentgens equivalent physical (rep).[41] The complexity of their interaction with tissue has been described by Zirkle.[97] Furthermore, they can induce radioactivity in various materials. While there is no evidence of a significant amount of induced radioactivity at the hypocenter (as attested by the absence of radiation effects in the Ishizuka military unit which had been sent to this area for rescue work after the explosion[47]), nevertheless, neutrons in their passage through the atmosphere produce a certain proportion of the highly penetrating gamma radiations. Since at any point there was a complex of radiations, the inclusive term "ionizing radiations" will be employed hereafter. There is justification for this in that no qualitatively different effects have been observed in the tissues upon exposure to the various types of radiations.[10,79,90] In each instance the damage inflicted is proportional to the quantity of energy absorbed, not to the quantity delivered.[90] It follows that the direct injury is localized to the sites where ionization occurs.[70]

The gamma rays merit special discussion, since they were probably by far the most important of the biologically damaging radiations emitted from the bomb at the instant of detonation and from the rapidly rising column of fission products. The higher the energy and the shorter the wavelength the greater is the penetrating power in tissue. Radiations of longer wavelength ("soft" gamma rays) tend to be absorbed in the superficial tissues, while some of those of shorter wavelengths may pass entirely through the body with little or no absorption. Thus the wavelength mixture as well as the distance from the explosion will determine the localization and extent of the greatest damage. During the explosion of the atomic bomb a spectrum of gamma rays of widely varying wavelengths was emitted. The proportions of the gamma ray energy of these various wavelengths in the radiations in Japan are not known. Moreover, the gamma rays are to some degree scattered by intervening materials, including air, thereby modifying the wavelength by the Comp-

ton effect,[87] with the result that very little is known about the quality of the radiations actually delivered to the body. Another factor of biologic importance is the dose rate. Within limits still to be determined, the more rapidly a given quantity of radiation is administered, the greater its injurious effect.[21,41] In the case of the atomic bomb the total duration of exposure was, at most, a few seconds, and probably by far the greatest dosage was delivered in a very small fraction of a second.

Although the exact nature, spectrum, and intensity of the ionizing radiations produced by the atomic bomb are incompletely known, their action upon the tissues is analogous to that of ordinary x-rays. The most striking changes were found in the skin, gastro-intestinal tract, testes, lymphatic system, and bone marrow. As a consequence of the direct damage to marrow, there resulted all of the tissue changes characteristic of aplastic anemia and of the associated infection. Thus, again, direct and indirect effects were manifest.

As to the range of the radiation effects, it may be stated that severe evidences of radiation injury were rare beyond 1500 yds. from the hypocenter, if they existed at all.

## Clinical Classification

Patients with radiation injury fall into four major groups which will receive brief discussion. The clinical observations are presented in detail in the body of the Medical Report.[47]

Group I: Patients dying in the first and second weeks.

Group II: Patients suffering severe symptoms or dying in the third, fourth, fifth, and sixth weeks.

Group III: Patients dying after the sixth week.

Group IV: Mild cases.

*Group I.* The factors responsible for death during the first 2 weeks may be: (1) An unusually high dosage of ionizing radiations either because of proximity to the bomb, or because of lack of efficient shielding. (2) An unusual susceptibility to ionizing radiations. Individual as well as species variations in susceptibility have often been observed.[38] (3) Concomitant severe thermal or traumatic injuries, or intercurrent infections, or causes of death not directly connected with the bombing. Multiple injuries were the rule.

With the exception of this last sub-group, which will be ignored for the present, many patients suffered during the first few days from a fatal illness that to the Japanese medical observers at first seemed mysterious,

until it was realized that they were dealing with the syndrome of "radiation sickness." The signs and symptoms in general resembled those found in animals after exposure to massive doses of ionizing radiations,[69] and probably represented largely the direct effects of these radiations, complicated in some instances by infection.

Patients complained of nausea and vomiting, often within ½ hour of the bombing, or during the succeeding hours or days. This was followed shortly by anorexia, malaise, severe diarrhea that in a few instances became sanguineous, intense thirst, and fever that ascended step-wise day by day. Death ensued in coma or delirium within the first 2 weeks. Leukopenia, especially lymphopenia, was found as early as the first day after the bombing in some of these patients, but others had no leukopenia at the time of death as late as 7 days after the bombing. Thrombocytopenia and an increasingly severe anemia appeared in that order, but usually not until after the second week.

In this early group there was already histologic evidence of radiation effect upon the hair follicles, gastro-intestinal tract, lymphoid tissues, bone marrow, and gonads, but neither epilation nor purpura had become clinically manifest in the vast majority of patients.

*Group II (Patients Dying During the Third, Fourth, Fifth, and Sixth Weeks, or Surviving Severe Clinical Symptoms).* In group II there were not only the clinical evidences of the direct damage by ionizing radiations such as epilation, but also the manifestations of aplastic anemia consequent upon destruction of the bone marrow. Bacterial infection, an indirect result of the radiation, was, as usual, responsible for the necrotizing lesions characteristic of the aplastic anemia. Purpura was now a frequent sign. Several factors were probably concerned in the pathogenesis of this condition: at first, probably the appearance in the blood of a substance with the properties of heparin[4]; later, thrombocytopenia which often reached levels below 10,000 per cmm.; and possibly also infection and vitamin deficiency with their effect on capillary fragility.

The usual sequence of events was as follows: Nausea and vomiting on the day of the bombing were the first evidences of the disease, followed by any or all of the symptoms characteristic of group I, but in milder form and persisting for only a few days. There was then a complete remission, until the appearance of epilation some 2 weeks after the bombing. Approximately 5 days after this, accompanied by increasing malaise, there was a daily ascending unremittent fever. At approximately the same time pharyngeal pain might appear or it came somewhat later. Petechiae and ulcerative lesions of the skin, lips, mouth, and pharynx became manifest within a few days after onset of the febrile episode.

Sanguineous diarrhea, associated with an ulcerative gastritis and enteritis, was frequently a prominent symptom at the height of the disease and sometimes appeared very early, as previously described. Leukocytes and platelets reached very low levels at the time of the fever and there was often severe anemia. The patient usually died within 1 or 2 weeks of the onset of the fever, approximately 1 month after the bombing.

Some patients exhibiting all or several of the symptoms of purpura, gingivitis, and severe or even necrotizing pharyngitis survived after a febrile period. Pharyngitis ceased before, petechiae before or during, and oropharyngeal lesions usually after the end of the febrile period. Recovery was associated with an increase in the circulating leukocytes and platelets. Many of these patients remained in an anemic and generally debilitated condition for long periods. In survivors the red blood cell count tended to fall slowly for some weeks after the end of the severe illness.

*Group III (Patients Dying after the Sixth Week).* In some members of group III in whom the bone marrow failed to recover or exhibited a maturation defect, the symptoms previously described continued and the patients died after a chronic illness. Patients with severe symptoms who survived beyond the sixth week, but who ultimately succumbed, usually were emaciated.

More commonly, with late fatality, the marrow tended to recover toward the end of the sixth week, and concomitantly most of the striking manifestations of the aplastic anemia, such as purpura, disappeared, but the patient nevertheless died of pneumonitis or enteritis—either a new illness of sudden onset, or an exacerbation of a smoldering lesion that had its inception during the earlier leukopenic phase. In these patients there was now a leukocytosis and the lesions contained an abundance of polymorphonuclear cells. There was usually no longer a marked thrombocytopenia, but anemia often was profound.

*Group IV (Mild Cases).* Persons who were situated near the limit of the range of the radiation, or who, although close to the center, were shielded by heavy buildings, manifested mild effects. In some, who were otherwise completely asymptomatic, leukopenia was discovered during a routine blood count. Some merely complained of anorexia and malaise. Diarrhea was a common complaint. Others had mild or even severe epilation without other symptoms. When, however, purpura or oropharyngeal lesions appeared, the patients usually also had epilation and passed through a febrile illness of varying degrees of severity such as was described in its most serious form in group II.

Most patients with the milder symptoms recovered completely. There were some, however, who had not regained their feeling of well being even 3 months after the bombing. A few of these people had a persistent leukopenia of approximately 3,000 at the time that the Joint Commission left Hiroshima (January, 1946). A moderate anemia was more common. What rôle dietary factors played in the anemia is not clear nor is there any information concerning how long the depression of the bone marrow could persist.

The important symptoms of the severest cases in the various groups are epitomized in Table II, and the anatomic findings are summarized in Table III.

TABLE II

*Clinical Manifestations of Severe "Radiation Effect"*

| Manifestation | Group | | |
|---|---|---|---|
| | 1st and 2nd weeks | 3rd to 6th weeks | After 6th week |
| Epilation | o | + | + |
| Petechiae | o | + | o |
| Necrotic gingivitis and oropharyngitis | o | + | o |
| Diarrhea | + | +* | +† |
| Pneumonitis | o | +* | +† |
| Leukopenia | + | + | o |

* Lesions usually do not contain polymorphonuclear leukocytes.

† Lesions usually contain polymorphonuclear leukocytes.

Nausea and vomiting, occurring soon after the bombing, were frequent among those who later showed other evidences of radiation effect.

Fever was a common finding in all groups before death.

## SYSTEMATIC SURVEY OF THE LESIONS

In the preliminary clinical survey it has been brought out that the character of the lesions was dependent on three important factors: the date of death, shielding and distance from the bomb, and the presence of severe thermal or mechanical injury.

The possible significance of the interval between radiation injury and death in relation to dosage and susceptibility has already been considered. It is among patients dying in the first 2 weeks that the direct radiation effects as seen histologically are least obscured by the infections that are consequent upon aplastic anemia. During the month following this initial period the lesions are those of aplastic anemia of any cause together with some persistent identifiable direct radiation effects. The hemorrhages observed during this interval and for some time beyond may have a complex pathogenesis as will be outlined. After the sixth week most deaths can be considered accidents of overwhelming respiratory or enteric infection, since the bone marrow usually has recovered by this time, although it remained aplastic in occasional patients.

TABLE III

*Important Anatomic Changes in Severe "Radiation Effect"*

| Tissue | Group I<br>Patients dying in weeks 1 and 2 | Group II*<br>Patients dying in weeks 3, 4, 5, 6 | Group III†<br>Patients dying after week 6 |
|---|---|---|---|
| Adipose tissue | Usually no depletion | Occasionally depletion | Usually depletion |
| Lung | Occasional hemorrhage and edema | Necrosis and hemorrhage | Focal necrotizing or organizing pneumonitis |
| Bone marrow | A. Hypoplasia | Usually<br>A. Hypoplasia<br>Occasionally<br>B. Marked reticulum hyperplasia<br>C. Focal myeloid regeneration<br>D. Marked myeloid hyperplasia | Usually<br>C. Focal myeloid regeneration<br>D. Marked myeloid hyperplasia<br>Occasionally<br>A. Hypoplasia<br>B. Marked reticulum hyperplasia |
| Lymph nodes and spleen | Extreme decrease of small lymphocytes | As in group I, and atypical mononuclear cells | As in group II, and occasionally regeneration of lymphoid tissue |
| Gastro-intestinal tract | Atypical mitotic figures and epithelial cells | Necrosis, hemorrhage, and ulceration | Necrosis and ulceration |
| Neck organs | Atypical mitotic figures and epithelial cells | Necrosis, hemorrhage, and ulceration | Focal necrosis and ulceration |
| Skin | Unknown | Petechiae and necrosis, atrophy of hair follicles | Regeneration of hair follicles; usually no other changes |
| Gonads (especially testis) | Incipient atrophy | Severe atrophy | Extreme atrophy |

* No polymorphonuclear cells in lesions.

† Polymorphonuclear cells in lesions.

No distinction is made in this table between the direct effects of ionizing radiations and the indirect effects resulting from infection, etc. These are discussed in the text.

In others, despite hyperplasia of the marrow, the peripheral blood may continue to show aplastic anemia.

In dealing with radiation, shielding and distance factors are of prime importance. The range of effects was investigated in a large-scale clinical study in which both symptomatic and laboratory evidence was evaluated.[47] With rare exceptions, severe effects were confined to a radius of 1500 yds. about the hypocenter. The exceptions may represent inaccuracies of geographic localization, or possibly persons with an unusual susceptibility to radiation. Inaccuracies are inevitable when dealing with large numbers of persons or records, especially since some of the patients were gravely ill or unconscious and the history was obtained indirectly.

Patients with severe burns or mechanical injuries were almost never examined post mortem by the Japanese during the emergency, unless there was also evidence of radiation effect. The factors of severe burns or trauma must, however, be considered in classifying the cases since they may, by virtue of concomitant shock, infection, and other mechanisms, have contributed to the pathogenesis of various lesions found at necropsy. A "severe burn" was considered to be any of the following: (1) a first degree burn involving more than 20 per cent of the area of the body, (2) a second degree burn involving more than 10 per cent of the surface, (3) a third degree burn involving more than 2 per cent of the surface.

Since the purpose of the systematic survey is to present the pathologic data objectively, a classification of the cases has been made according to three major factors, as follows:

A. By date of death
   1. Within the first 14 days
   2. Between the 15th and 42nd day
   3. After the sixth week

B. By distance
   1. Within 1500 yds.
   2. Beyond 1500 yds.

C. By the occurrence of severe burns
   1. Without severe burns
   2. With severe burns

To simplify the systematic description of the material, a 3-digit numerical classification will be employed, one digit being drawn from each of the three major classifications as outlined above and in the order in which they have been presented. Thus the first digit refers to date of

death according to the three subheadings under that classification, the second refers to distance under the two categories that have been established, and the third according to whether or not the patient had suffered severe burns. Thus, "212" indicates a patient who died between 15 and 42 days after the bombing, who was within 1500 yds. of the center, and who had severe burns.

The cases that came under study are classified in Table IV according to the scheme just outlined. It is apparent that the 16 Nagasaki cases whose distance from the bomb is recorded are all in group III. The others will be used only for general comparison with the Hiroshima material in relation to time of death.

TABLE IV

*Number and Types of Cases from Which Necropsy Specimens Are Available*

| Number of cases (Hiroshima) | Types of cases | | | Number of cases (Nagasaki) |
|---|---|---|---|---|
| | Identifying class number | Presence of burns | Distance | |
| | | Group I (Dead before the 15th day) | | |
| 3* | 111 | No burns | Within 1500 yds. | 1 |
| 8 | 112 | Burns | | |
| 1 | 122 | Burns | Beyond 1500 yds. | |
| | | Group II (Dead 15th to 42nd days) | | |
| 58 | 211 | No burns | Within 1500 yds. | 52 |
| 5 | 212 | Burns | | |
| 2 | 222 | Burns | Beyond 1500 yds. | |
| | | Group III (Dead after the 42nd day) | | |
| 9 | 311 | No burns | Within 1500 yds. | 6 |
| 1 | 312 | Burns | | 3 |
| 4 | 321 | No burns | Beyond 1500 yds. | 1 |
| 3 | 322 | Burns | | 6 |
| | | Data not given | | 7 |
| 94 | | Grand total | | 76 |

* Material from additional Hiroshima cases, presumably in sub-group 112, although the distance was not recorded, is employed for illustrating certain lesions.

Certain gaps resulting from the fragmentary nature of some of the material will be evident in the attempted reconstruction of the sequence of events in the various systems. Obviously the reconstruction, based

TABLE V

*Hiroshima, Group I: Clinical Data on Patients Dying before the 15th Day*

| Autopsy K no. | Day of death | Age | Sex | Distance (yds.) | Burns | Lacerations and contusions | Nausea or vomiting related to bombing | Diarrhea | Other signs or symptoms | White blood cells | Albuminuria | Fever |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sub-group 111** | | | | | | | | | | | | |
| 2 | 4 | 24 | M | 800 | ± | + | + | o | Weakness, excitement, then coma | | | |
| 5 | 6 | 39 | M | 1000 | ± | + | o | o | Headaches, simple fracture of femur | | | +? |
| 9 | 8 | 25 | M | 1500 | ± | + | + | | | 7500 (7) | + | +? |
| **Sub-group 112** | | | | | | | | | | | | |
| 1 | 3 | 13 | M | 1300 | ++ | | | | | | | |
| 3 | 5 | 15 | M | 1000 | ++ | | + | + | | 9500 (7) | | + |
| 4 | 6 | 32 | M | 1000 | ++ | | o | + | | | | +++ |
| 6 | 6 | 13 | F | 1500 | +++ | | + | + | Sleeplessness | | | |
| 7 | 7 | 34 | M | 1000 | + | | o | + | "Cerebral symptoms" | | | ++ |
| 8 | 8 | 29 | M | 1200 | ++ | + | + | | Simple fracture of femur | | | +? |
| 11 | 8 | 25 | M | 1200 | +++ | | o | o | | 5500 (7) | + | +++ |
| 12 | 9 | 33 | M | 700 | +++ | | + | + | | | | +? |
| **Sub-group 122** | | | | | | | | | | | | |
| 10 | 9 | 24 | F | 2000 | ++ | | | + | Excited mental state, then coma | 9500 (8) | + | ++ |

No notation = no information given in record.
o = sign or symptom was stated to have been absent.
Burns: ±, minor burns; +, ++, +++, severe burns.
White blood cells: Figure in parentheses indicates day on which stated count was made.
Fever: +?, fever present but temperature unstated; +, fever to 39° C.; ++, fever to 40° C.; +++, fever to 41° C.

as it was on surviving material and recorded information, had certain archeologic aspects. Since the deficiencies in the records of the early cases are particularly lamentable, a special effort is made to present them in all available clinical and anatomic detail.

### *Group I: Patients Dying within the First 14 Days*

In group I there already were profound evidences of radiation effects histologically, but epilation, purpura, and many of the spectacular indirect effects of aplastic anemia that are occasioned by the associated infections had not yet appeared. For this reason the deaths were at first clinically obscure.

The specific clinical data in the 12 patients in group I who were necropsied are recorded in Table V. There was no evidence of leukopenia at the end of the first week in the 3 patients for whom counts are available and who were stated to have been within 1500 yds. of the hypocenter. In many others, however, severe leukopenia had already

TABLE VI

*Hiroshima, Group I: Heart*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Gross specimens available | 2 | 8 | 1 |
| Histologic specimens available | 2 | 8 | 1 |
| Epicardial hemorrhages | 2 | 6 | |
| Perivascular edema | 1 | 2 | 1 |
| Thrombus in venule | | 1 | |
| Plasmacytic or mononuclear cell infiltration of myocardium | | 1 | |
| Plasmacytic or mononuclear cell infiltration of endocardium | | 1 | |

developed in the first few days. The actual count may have been masked by severe dehydration. Differential counts are not available for these 3 patients.

The 3 patients of sub-group 111, in whom both traumatic and thermal injuries were slight, are of particular interest since they seem to have succumbed purely to the effects of radiation. They were no closer to the bomb than many others who survived. Their only protection was the wood and pantile of the Japanese buildings in which they were at the time of the explosion. The mechanism of death will be considered in the general discussion that follows the systematic descriptions.

*Heart (Table VI).* Petechiae of the epicardium were commonly found grossly. Microscopically, there occasionally was evidence of edema about the vessels of the myocardium. In one patient, who had been severely burned, there was plasma cell infiltration just beneath the

lining cells of the endocardium, and focal necrosis of the myocardium with mononuclear infiltration of the myolemma. Such changes cannot be considered as specific radiation effects, since they have been described in patients with many kinds of infection[81] and with burns.

*Lungs (Table VII).* In most instances the pulmonary changes were those of focal atelectasis and emphysema, and edema of the interstitial tissues (Fig. 20). There was no certain evidence of blast effect, although hemorrhages were observed in one instance. Among the 8 patients of sub-group 112 there was one with "neutropenic pneumonia"—focal necrosis and hemorrhage without polymorphonuclear infiltration—and another with focal pneumonia of the usual type with a heavy polymorphonuclear leukocytic exudate. In the latter instance the marrow

TABLE VII

*Hiroshima, Group I: Lungs*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Histologic specimens available | 3 | 8 | 1 |
| Focal atelectasis and emphysema | 1 | 6 | 1 |
| Edema of interstitial tissue | 2 | 6 | 1 |
| Edema fluid in alveoli | 1 | | |
| Thrombi or emboli in pulmonary arterioles | 1 | 1 | |
| Focal parenchymal hemorrhages | 1 | | |
| Focal "neutropenic pneumonia" | | 1 | |
| Focal necrotizing pneumonia with polymorphonuclear cells | | 1 | 1 |
| Additional observations | | | |
| Disseminated fibrocaseous nodules | | | 1 |
| Fibrous pleural adhesions | | 3 | 1 |
| Ghon's complex | | 1 | |
| Apical fibrous scar | | 1 | |

was hyperplastic although the patient (K-12) was stated to have been 700 yds. from the hypocenter. The lymphoid tissue of the lungs partook of the general atrophy which will be described. Hemorrhages tended to be more numerous in patients dying after the second week.

*Hemopoietic Organs in General.* In the first few days in heavily irradiated patients there was a very rapid disappearance of lymphocytes and myeloid elements, followed by proliferation of atypical cells. Some of these resembled plasma cells and others, of larger size, were intermediate in structure between the plasma cells and the large elements of the reticulum. There appeared also huge cells with irregularly folded nuclei resembling Reed-Sternberg cells.

*Spleen (Table VIII).* The weight of the spleen usually was less than 100 gm. In general, the capsule was wrinkled and the organ soft. The cut surface was dark red and pulpy, but little material was yielded upon

scraping. Malpighian corpuscles were invisible to the naked eye, but the trabeculae were distinct.

Microscopically, the reduction in size was accounted for by the fact that the lymphocytes had almost completely disappeared. Malpighian corpuscles were only vaguely outlined by the whorled structure of the

TABLE VIII

*Hiroshima, Group I: Spleen*

| Observations | Sub-group | | |
|---|---|---|---|
| | III | II2 | I22 |
| Histologic specimens available | 3 | 8 | I |
| Weight less than 100 gm. | I of 2* | 4 of 6* | I |
| Rupture | | I | |
| Decrease of lymphocytes | 3 | 5 | I |
| Absence of germinal centers | 3 | 5 | I |
| Atypical mononuclear cells | 3 | 6 | I |
| Hyaline change in vessels | 3 | | |
| Heavy mature plasma cell infiltration | | I | |
| Perifollicular hemorrhage | | I | |
| Numerous eosinophils | | I | |

* The weights of the other spleens were not recorded.

collagenous and reticular tissue that appeared as a collapsed network about the central arterioles (Figs. 28 and 29). The subendothelial tissue of the latter contained a brightly acidophilic, refractile material. The endothelium itself was well preserved. In the immediate vicinity of these central vessels were found only a few small mononuclear cells, some of which had the structure of plasma cells. The nuclei of some of the latter as well as those of certain larger cells, presumably of the germinal center, were in process of lysis. The cytoplasm of such cells had shrunk into an opaque granular mass. Among these cells there were many apparently empty spaces. The process thus appeared to be one of necrobiosis and there was little evidence of phagocytosis of lymphoid elements. However, erythrophagocytosis and hemosiderosis of moderate degree were in evidence in all of these spleens (Fig. 31). Perifollicular and intrafollicular hemorrhages were noted in one instance (Fig. 30). There was no apparent change in the fibro-elastic structure of the capsule and trabeculae. At the insertions of the latter upon the former there were deep indentations of the surface.

In most patients, despite the atrophy of the lymphoid tissue, there was proliferation of atypical cells (Figs. 30 to 32, and 40). This was already in evidence, in the earliest available specimen, on the third day after the bombing and might become so massive as to increase the weight of the spleen. The atypical cells were irregular in shape and size, and possessed neutrophilic or basophilic cytoplasm and generally hyper-

chromatic nuclei with thick nuclear membranes and prominent nucleoli. Some resembled reticulum cells, and others lymphoblasts or the "splenic tumor cells" described by Rich, Lewis, and Wintrobe.[72] Some cells were so bizarre as to suggest the Reed-Sternberg cells of Hodgkin's disease (Fig. 32). Many cells were in mitosis and some of the mitotic figures were multipolar or otherwise atypical.

In one spleen of sub-group 112, there were numerous mature plasma cells and large spindle-shaped or polygonal elements containing prominent eosinophilic granules. The pathogenesis of this change is unknown. In another patient of this sub-group, there was rupture of the spleen with a slight quantity of blood in the peritoneal cavity. This patient had sustained trauma to the head, and probably the splenic lesion was also of traumatic origin.

*Lymph Nodes (Table IX).* The essential changes in the lymph nodes resembled those seen in the spleen. Germinal centers were not seen and

TABLE IX

*Hiroshima, Group I: Lymph Nodes*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Histologic specimens available | 0 | 4 | 0 |
| Decrease of lymphocytes | | 3 | |
| Absence of germinal centers | | 3 | |
| Atypical mononuclear cells | | 2 | |

there was a striking reduction of the numbers of small lymphocytes. Thus little more than the reticular skeleton of the node remained. This compaction of the reticulum cells was clearly evident as early as the fifth day, and was particularly striking in a node from a patient who died on the tenth day (Fig. 44). Numerous mast cells were found among the reticulum cells. At 10 days a few large cells with the structure of lymphoblasts and some bizarre mononuclear elements resembling the atypical cells of the spleen had appeared. An occasional large cell was found in mitosis. These proliferative changes became more prominent in time, as will be evident from study of the nodes in group II.

*Bone Marrow (Table X).* Disappearance of the myeloid tissue and the presence of atypical cells within the first week after the bombing is indicated by the study of aspirated vertebral marrow,[43,52] carried out by the Japanese and later reviewed by us, in patients who may be assumed to have received a considerable dose of radiation. The failure of delivery of leukocytes to the peripheral blood was confirmed by their absence in exudates in obviously infected lesions seen at necropsy.

TABLE X

*Hiroshima, Group I: Bone Marrow*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Long bones | | | |
| Histologic specimens available | 1 | 3 | 1 |
| Hypoplasia | 1 | 1 | |
| Marked myeloid hyperplasia | | 2 | 1 |
| Flat bones | | | |
| Histologic specimens available | 0 | 2* | 0 |
| Hypoplasia | | 1 | |
| Marked focal reticulum hyperplasia | | 1 | |

* Distance is not known in these 2 patients. Since the histologic changes in the tissues are so striking an indication of radiation effect, these patients are assumed to have been within 1500 yds.

The earliest histologic sections of marrow came from patients dying on the sixth day. Unfortunately, these were derived from long bones, where active hemopoiesis is usually not in progress in the adult. Even in these marrows there already was evidence of proliferation of the reticulum and of the formation of plasma-like cells, a process which became increasingly prominent for a time after the second week. Thus in the marrow derived from the femur or humerus of a 39-year-old man who died on the sixth day, there were small amounts of cellular tissue among the fat cells, and widely dilated blood vessels (Fig. 35). Many of the cells resembled plasma cells. In the hematoxylin and eosin preparations they had wine-colored, deeply staining cytoplasm and pyknotic nuclei. There also were other elements, intermediate in size between them and the large stellate elements of the reticulum. Some of these still retained the phagocytic property since the cytoplasm was filled with erythrocytes. Occasionally a cell resembling a reticulum cell was found to have an enormous amount of cytoplasm and a much folded vesicular nucleus. These cells were not nearly so large as the megakaryocytes and the cytoplasm was more basophilic. Only rarely was a myelocyte found at this time. There was nothing that suggested well-functioning hematopoietic tissue. Evidence of the functional insufficiency of the marrow in this case was the total absence of leukocytes in a small portion of burned skin (Fig. 13).

The first specimen of marrow from a flat bone, the sternum, was from a patient of sub-group 112, dead on the tenth day (Fig. 58), whose distance from the bomb, unfortunately, is unknown. Typical myeloid tissue was not in evidence. In its place there were numerous plasma cells and some larger atypical cells which often were found in long strings, applied adventitially to the thin-walled vessels of the marrow.

Another patient (Fig. 59), who died on the twelfth day and whose distance from the bomb is again unknown, exhibited in sections of sternum a much more striking focal hyperplasia of reticulum together with numerous plasmacytoid cells. This type of response, termed "marked focal reticulum hyperplasia," is discussed in group II and its description will not be further elaborated here.

In 2 patients, K-11 and K-12, stated to have been at 1200 and 700 yds., respectively, and who had sustained severe burns, there was myeloid hyperplasia in the long bones with "shift to the left." Granting the position of these patients to have been correctly stated, this occurrence represents an individual variation in response. Had there been no burns these patients might have been among the survivors.

*Gastro-intestinal Tract (Table XI).* The changes observed in the gastro-intestinal tract during the first 2 weeks included the occasional appearance, by the fourth day, in the earliest available material, of atypical epithelial cells and petechiae, and after the seventh day of occasional ulcerative lesions.

TABLE XI

*Hiroshima, Group I: Gastro-intestinal Tract*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Stomach | | | |
| Gross specimens available | 3 | 8 | 1 |
| Histologic specimens available | 1 | 7 | 0 |
| Petechiae | 2 | 3 | 1 |
| Acute ulcer | | 1* | |
| Plasma cell infiltration | 1 | 1 | |
| Atypical epithelial cells | 1 | | |
| Small intestine | | | |
| Gross specimens available | 2 | 8 | 1 |
| Histologic specimens available | 2 | 5 | 1 |
| Ulcers and hemorrhage | | 1* | |
| Atypical epithelial cells and mitotic figures | 2† | 1 | |
| Petechiae | | | 1 |
| Large intestine | | | |
| Gross specimens available | 1 | 8 | 0 |
| Superficial ulcers | 1* | 1* | |
| Additional observations | | | |
| Ascariasis | 2 | 3 | |

* Gross only.

† There was also a Nagasaki case, K-175, dying on the 11th day, with similar changes in the epithelium, together with ulcers of the intestines.

Epithelial changes were demonstrated in a section of ileum from a patient who died on the sixth day. This material was well fixed soon after

death. The epithelium of the surface had in part sloughed, but without loss of substance of the underlying connective tissue. That which remained was extremely irregular in size and shape. Many epithelial cells were spindle-shaped and some possessed vesicular nuclei with large clumps of chromatin and irregular masses of basophilic cytoplasm (Fig. 80). Few small lymphocytes were left in the mucosa and there were relatively large numbers of plasma cells together with reticulum cells. The mucosa was edematous. The changes in the intestine of K-2, who died on the fourth day, were similar; a tripolar mitotic figure is illustrated in Figure 81. Such epithelial changes were observed in the small intestine of 3 patients, and once in the stomach. They closely resemble lesions found in animals experimentally exposed to gamma rays.[27] Either these atypical epithelial cells are not long viable, or else patients receiving a dose of radiation large enough to produce them do not live long, since they were not observed in patients necropsied after the second week.

Ulcerative lesions were not observed before the seventh day. In one patient at Nagasaki who died on the eleventh day, both bizarre, occasionally binucleated epithelial cells and focal necrosis of the mucosa and submucosa were observed (Figs. 82 and 83). Numerous bacterial masses were found in the tissue, but there were no leukocytes. Both the direct effects of ionizing radiation and the absence of the leukocytic defense mechanism may have contributed to the development of such ulcerative lesions.

Atrophy of lymphoid tissue was found in all instances in which there had been exposure to radiation. Heavy plasma cell infiltrations, however, were found in several instances. The essentially similar changes in the pharynx and tongue are described on page 880.

*Pancreas.* No significant changes were found in the pancreas.

*Liver (Table XII).* The liver was of the usual size. Microscopically, the cells appeared finely granular and displayed no fatty changes. The

TABLE XII

*Hiroshima, Group I: Liver*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Histologic specimens available | 3 | 8 | 1 |
| Giant nuclei in pericentral hepatic cells | 3 | 1 | |
| Central congestion, slight | 3 | 8 | 1 |
| Edema of pericentral connective tissue | 3 | | |
| Heavy plasma cell infiltration of portal zones | | 1 | |

nuclei of some of the cells near the central vein were large and hyperchromic. The central parts of the hepatic cell cords were narrower and the sinusoids there were more widely dilated than elsewhere. The walls

of many central veins appeared to be thick and to consist of loosely arranged collagenous material which extended outwards in strands among the cell cords (Fig. 93). This change is interpreted to be the result of edema. The Kupffer cells were not strikingly enlarged nor did they contain unusually large quantities of pigment. In one instance, from sub-group 112, there was a heavy periportal infiltration of plasma cells.

*Kidneys (Table XIII).* Hemorrhages were observed beneath the mucous membrane of the renal pelvis in most instances; otherwise there was nothing remarkable grossly.

TABLE XIII

*Hiroshima, Group I: Kidneys*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Gross specimens available | 3 | 8 | 0 |
| Histologic specimens available | 2 | 7 | 0 |
| Hemorrhages of pelvis | 2 | 6 | |
| Cloudy swelling | 2 | 7 | |
| Small and large mononuclear cells in corticomedullary sinusoids | 1 | 2 | |
| Heavy plasma cell infiltration | | 1 | |

Except for cloudy swelling of the epithelial cells of the convoluted tubules in many cases, there were no significant microscopic changes. The blood vessels did not contain fibrinoid or hyaline material. In the sinusoids of the corticomedullary junction in several sections there were remarkable collections of small and large mononuclear elements (Fig. 96). Some were small and had almost spherical, deeply basophilic nuclei and scanty basophilic cytoplasm. These resembled small lymphocytes. Mingled with them were much larger elements whose cytoplasm was neutrophilic and at times vacuolated. The nucleus was small, ovoid or bean-shaped, and its chromatin was delicately reticular. These cells had the structure of macrophages. Other cells possessed deeply basophilic cytoplasm. Their nuclei exhibited a coarse network of chromatin, with prominent nucleoli. Such cells resembled "blasts." Occasionally some of the blast-like cells were attached to the walls of these sinusoids, and transitional forms were seen which were flattened and gave the impression of being endothelial cells in process of becoming detached and rounded. Occasionally a cell was found in mitosis. There were no cells that had the appearance of mature normoblasts nor was there granulation of the cytoplasm to indicate that they were myelocytes. We have noted similar cells in similar positions in various other conditions. They have been noted also in scrub typhus.[2] In one patient who had severe burns there was a very heavy plasma cell infiltration about the glomeruli. These

cells occurred also in large numbers elsewhere in the tissues of this patient, as in the spleen and heart.

*Ureters and Bladder.* No changes were observed in the ureters and bladder.

*Testes.* Grossly, in the 4 instances in which material was available, the tubules of the testes strung out easily and no changes in size or consistency were noted.

Microscopically, in 2 of the 3 specimens available, there were striking changes, even after 4 days. The germinal epithelium had largely sloughed from the basement membrane. Sertoli cells had become prominent and in some places formed a continuous sheet. The spermatogonia were largely in the lumina of the tubules. Many were still found in mitosis, but spermatids and spermatozoa already seemed diminished in numbers (Fig. 98). Many spermatogonia and their derivatives possessed pyknotic nuclei. The Leydig cells had their usual appearance. The rete testis contained not only spermatozoa but remnants of their precursors that had sloughed away in various stages of necrosis. Such changes were noted in 2 of the 3 specimens available for microscopic examination, one each from sub-groups 111 and 112. In another of sub-group 112 the tissue was poorly preserved and no definite microscopic changes were discovered.

*Ovaries.* In the ovaries of one patient, 13 years of age, who probably had not reached the menarche, there were numerous primordial follicles and small follicular cysts, but no developing follicles or corpora albicantia. No other specimens were available for histologic study.

*Brain (Table XIV).* Striking congestion of the vessels was usually described upon gross examination of the brain. In one instance, there were superficial contusions and hemorrhages in the occipital and temporal lobes, probably of traumatic origin. In another, capillary hemor-

TABLE XIV

*Hiroshima, Group 1: Brain*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Gross specimens available | 2 | 7 | 0 |
| Histologic specimens available | 2 | 5 | 0 |
| Congestion | 2 | 4 | |
| Edema of pia | | 2 | |
| Multiple contusions with hemorrhages | 1 | | |
| Capillary hemorrhages | | 1 | |

rhages were found. Histologically, neither cellular exudate nor gliosis was in evidence and the ganglion cells, including the Purkinje cells, were well preserved.

*Adrenals (Table XV).* In the adrenal glands of even the earliest cases there often was evidence of a decrease in cortical lipoid. Grossly, this was shown by the pale yellow-gray, rather than orange-yellow, color of the cortex and by its remarkable translucency.

TABLE XV

*Hiroshima, Group I: Adrenals*

| Observations | Sub-group | | |
|---|---|---|---|
| | 111 | 112 | 122 |
| Histologic specimens available | 3 | 6 | 1 |
| Atrophy of cortex* | 1 | 3 | 1 |
| Fibrinous material in peri-adrenal fat | 1 | | |
| Heavy plasma cell infiltration | | 1 | |
| Hyaline change of capsular arterioles | | 1 | |

* Usually with special involvement of the zona glomerulosa.

Microscopically, as early as the fourth day, there was evident a striking atrophy of the cells in the outer cortical zone, and edematous collagenous material extended inward from the capsule (Fig. 116). This change resembled that of the pericentral tissues of the liver (compare with Fig. 93). The other cortical cells also showed relatively little vacuolation and had finely granular cytoplasm. There was an abundance of finely granular brown pigment in the reticularis. The medullary substance was preserved in its typical histologic appearance. In another case, which was not otherwise unusual, fibrinous material had appeared in the septa of areolar tissue that traversed the periadrenal fat. Hyaline changes of the arterioles of the capsule were found in another. A third adrenal gland, from a severely burned patient, showed a striking infiltration of plasma cells.

*Thyroid Gland.* No changes were detected grossly or microscopically in the thyroid gland.

*Parathyroid Gland.* The one parathyroid gland available, from a patient in sub-group 112, was found to consist almost entirely of chief cells of typical appearance.

*Pituitary Body.* Three sections were available from the pituitary body, one from a patient in sub-group 111 who died on the fourth day. Despite poor fixation, it was evident that acidophilic cells predominated, which is to be expected in a 24-year-old man. The other two, one from a female and the other from a male patient, likewise showed a predominance of acidophilic cells.

*Thymus.* Interpretation of changes in the thymus always is difficult. The structure of the organ in a 13-year-old boy who died on the third day resembled that of the lymphoid tissue. The connective tissue was

edematous. The lobules of the parenchyma consisted of stellate reticular elements supporting smaller cells with ovoid nuclei which likewise had stellate processes. Small round cells indistinguishable from lymphocytes were rare, although they should be present in large numbers at this age. Occasional mononuclear cells with eosinophilic granules in the cytoplasm were found. Hassall's corpuscles were numerous but small. They were anuclear at their centers in most instances, and some had become calcified.

In other specimens from this group, according to the gross descriptions, almost total atrophy of the organ had occurred, but no sections were available for study.

*Neck Organs.* Remarkable changes had occurred in the epithelium of the pharynx, tonsils, tongue, and esophagus of K-98, the single case available for detailed study.* Unfortunately, the distance from the bomb and other exposure factors are unknown. It was stated that this man had sustained trauma and burns. It may be presumed from the appearance of the lymph nodes and the sternal bone marrow (Figs. 44 and 58) that a massive dose of ionizing radiations was received.

In the *pharynx* of this patient the epithelial cells had become remarkably swollen, vacuolated, and fragmented as had their nuclei, and much of the epithelium had desquamated. The connective tissues were tremendously edematous and there was a striking lymphectasia. Scattered plasma cells and large mononuclear cells occurred in the areolar tissue. The lymphoid tissue had become remarkably atrophic here as elsewhere (Figs. 119 and 120).

In the *tongue* the epithelium consisted of enormous, bizarre epithelial cells whose cell boundaries were now difficult to distinguish (Fig. 121). Many of the nuclei had become multi-lobed and in each lobe there was a prominent nucleolus. Multiple minute nuclei, resembling the "micronuclei" observed as a colchicine effect,[14,80] were present in some large cells. Some cells had become separated from their neighbors and appeared as refractile, homogeneous, acidophilic masses. Thick layers of parakeratotic material were present on the surface. In the connective tissue underlying the epithelium there were dilated lymphatics and small, closely crowded, spindle-shaped fibroblasts.

The epithelial cells lining the crypts of the *tonsils* exhibited changes similar to those observed in the pharynx. Here also, the nuclei were vesicular, with prominent knots of chromatin. There was a remarkable alteration of the lymphoid tissue, which was represented largely by

* Sections of the tonsils from another patient exhibited only atrophy of the lymphoid tissue but no notable epithelial changes.

compacted spindle-shaped elements of the reticulum among which were suspended only a few mature lymphocytes. The substance of the tonsil had not become necrotic.

There were notable changes in the *esophagus*. In many places the squamous epithelium of the surface had been replaced by purple-staining, dull, necrotic material. Only the swollen remnants of a few squamous cells, as bizarre in their cytoplasmic and nuclear components as those in the tongue, could still be distinguished. In the immediately underlying tissue there was a striking degree of edema, which extended deeply among the bundles of striated muscle, and there also was dilatation of vessels. There was no leukocytic infiltration.

With certain qualities of radiation these mucous membranes are more prone to show demonstrable changes in the epithelium than the skin (Coutard[18]). Unfortunately, sections of skin from this patient (K-98) were not available.

The changes in the tissues of K-98 undoubtedly represent radiation effects. They are analogous to those in the intestine as shown in Figures 80 and 82. In the present instance, however, there were no atypical cells or mitotic figures in the stomach, which represents the only portion of the gastro-intestinal tract available in histologic sections.

*Skin.* Unfortunately, skin unaltered by thermal burns is not available from any patient dying during the first 2 weeks.

### *Group II: Patients Dying During the Third, Fourth, Fifth, and Sixth Weeks*

In group II, changes characteristic of radiation, such as epilation, testicular atrophy, and, particularly, damage to the hemopoietic tissues were at their peak. The most striking new developments were those associated with the infections that accompanied the aplastic anemia. All surfaces to which bacteria had access became the seat of foci of necrosis accompanied by hemorrhage. Ultimately there was evidence in many cases of generalization of the infection. If there was any leukocytic response, it was of plasma cell or mononuclear type. Extravasations of blood also occurred apart from any obvious local foci of infection in such organs as the kidney. The factors—heparin, platelets, bacteria, and vitamins—possibly concerned in the pathogenesis of the purpura are discussed elsewhere.[47] It is of note that the blood at necropsy often was observed to be in an unclotted state.

The salient clinical data relevant to the Hiroshima patients who ultimately were necropsied are recorded in Table XVI, in which all groups are compared.

TABLE XVI

*Recorded Clinical Data on Hiroshima Patients, Examined by Necropsy*

| Observations | | Group I | | | Group II | | | Group III | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sub-group | | | Sub-group | | | Sub-group | | | |
| | | 111 | 112 | 122 | 211 | 212 | 222 | 311 | 312 | 321 | 322 |
| Total number | | 3 | 8 | 1 | 58 | 5 | 2 | 9 | 1 | 4 | 3 |
| Male | | 3 | 7 | 0‡ | 46 | 5 | 1 | 5 | 1 | 3 | 2 |
| Female | | 0 | 1 | 1 | 12 | 0 | 1 | 4 | 0 | 1 | 1 |
| Well nourished | | | | | 42 | 4 | 1 | 4 | 0 | 0 | 0 |
| Poorly nourished | | | | | 16 | 1 | 1 | 5 | 1 | 4 | 3 |
| Burns | | 3* | 8† | 1† | 10* | 5† | 2† | | 1† | 1* | 3† |
| Mechanical injury | | 3 | 1 | | 33 | | | 5 | | | |
| Nausea and vomiting on day of bombing | | 2 | 4 | | 11 | | | | | | |
| Epilation | | 0 | 0 | 0 | 50 | 1 | | 6 | | 1 | 1 |
| Purpura | | 0 | 0 | | 38 | 1 | | 2 | | | |
| Ulcers or abscesses of skin | | 0 | 0 | | 3 | | | | 1 | | |
| Gingivitis (all) | | 0 | 0 | | 37 | | | 2 | | | |
| Gingivitis (necrotic) | | 0 | 0 | | 3 | | | | | | |
| Pharyngitis or tonsillitis (all) | | | | | 32 | | | 1 | | | |
| Pharyngitis or tonsillitis (necrotic) | | 0 | 0 | | 5 | | | | | | |
| Diarrhea (all) | | 0 | 5 | 1 | 24 | 3 | | 4 | | 3 | 1 |
| Diarrhea (hemorrhagic) | | | | | 11 | 1 | | 2 | | 2 | |
| Epistaxis | | | | | 6 | 3 | | 1 | | | |
| Rectal hemorrhage | | | | | 1 | | | | | | |
| Vaginal hemorrhage | | | | | 2 | | | | | | |
| Hemoptysis | | | | | 4 | | | 1 | | | |
| Fever (maximum) | To 39°C. | | 1 | | | | | | | | |
| | To 40°C. | | 1 | 1 | 21 | 3 | 1 | | | | |
| | Over 40°C. | | 2 | | 6 | 1 | | 2 | | | |
| Fever present, temperature unstated | | 2 | 2 | | 17 | | | | | | 1 |
| Lowest white blood cell count recorded | 0– 500 | | | | 20 | | | 1 | | | |
| | 501–1000 | | | | 6 | 2 | | 1 | | | |
| | 1001–1500 | | | | 2 | 2 | | | | | |
| | 1501–2000 | | | | | | | 1 | | | |
| | 2001–2500 | | | | 1 | | | | | | |
| | 2501–3000 | | | | | | | | | | |
| | Over 3000 | 1 | 2 | 1 | | | 1 | 3 | | 1 | |
| Lowest red blood cell count recorded | Less than 1.6 | | | | 2 | | | 3 | | | |
| | 1.6–2.0 | | | | | | | | | | |
| | 2.0–2.5 | | | | 9 | | | 1 | | | |
| | 2.6–3.0 | | | | 5 | | | | | 1 | |
| | 3.1–3.5 | | | | 6 | | | 1 | | | |
| | Over 3.5 | | | | 5 | 3 | 1 | 1 | | | |

* Slight.

† Severe.

‡ o indicates that the sign or symptom was not present. A blank space indicates that no observation was recorded in the clinical record. The incidence of any finding as stated in the table is minimal, since the basic information may be incomplete in some instances.

*Heart (Table XVII).* Epicardial hemorrhages were usually, and endocardial extravasations sometimes, present (Fig. 10) and occasionally there also were hemorrhages in the neighborhood of the conduction bundle (Fig. 16). Fluid blood, which did not clot upon standing, frequently was observed in the chambers of the heart and great vessels. Perivascular hemorrhages in the myocardium occasionally were present

TABLE XVII

*Hiroshima, Group II: Heart*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Gross specimens available | 55 | 5 | 2 |
| Histologic specimens available | 49 | 5 | 2 |
| Epicardial hemorrhages* | 33 | 3 | |
| Endocardial hemorrhages* | 6 | | |
| Fluid blood in chambers* | 8 | 2 | |
| Perivascular edema | 4 | | |
| Perivascular hemorrhages of myocardium | 7 | | |
| Thrombus in venule | | | 1 |
| Focal necrosis of myocardium | 1 | | 1 |
| Plasma or mononuclear cell infiltration of myocardium | 1 | | 1 |
| Plasma or mononuclear cell infiltration of endocardium | 7 | 1 | |
| Additional diagnoses | | | |
| Chronic verrucous endocarditis | 2 | | |

* Gross diagnosis.

and there sometimes was edema of the perivascular tissue, as observed in the specimens from patients dying before the end of the second week. In 5 instances, there was seen immediately beneath the endothelium of the chambers an exudate of plasma cells sometimes mingled with small and large mononuclear cells. These also were present in the myocardium (Fig. 21).

In 2 instances there was evidence of previous rheumatic disease, in the form of chronic verrucous endocarditis.

*Lungs (Table XVIII).* The characteristic gross lesion of the lungs in group II was that of focal necrosis centered upon minute bronchioles whose lining membranes had become necrotic. Surrounding these foci of necrosis were brilliant red zones of hemorrhage which had become confluent in some instances. The intervening parenchyma was translucent and pale, and exuded a large quantity of fluid which was only slightly cloudy. In some instances hemorrhage was predominant about extremely minute foci of necrosis (Fig. 19), but in others dull yellow or gray-green, opaque, rounded masses of necrotic tissue were surrounded by relatively narrow zones of extravasated blood (Fig. 17). Tuberculous lesions also may be surrounded by massive hemorrhages at this stage, so that vigilance was necessary in gross interpretation to avoid confusion with ordinary non-tuberculous necrosis (Fig. 18).

The pleura usually was the seat of extravasation of blood and was rendered thick and translucent by edema, which produced similar changes in the septa.

Histologically, these lungs had a characteristic structure to which the term "neutropenic pneumonia" has been applied. There was a striking degree of edema of the pleura and peribronchial and perivascular

TABLE XVIII

*Hiroshima, Group II: Lungs*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Histologic specimens available | 57 | 5 | 2 |
| Focal atelectasis and emphysema | 1 | 1 | |
| Edema of interstitial tissue (no other lesions) | 1 | | |
| Edema of alveoli | 1 | | |
| Focal parenchymal hemorrhages and edema | 11* | | 1 |
| Focal "neutropenic pneumonia" | 31 | 1 | |
| Focal necrotizing pneumonia with polymorphonuclear cells | 3 | 2 | |
| Focal tuberculous pneumonia | 2 | | |
| Fibrinous pleurisy | 4 | 1 | |
| Fibrinopurulent pleurisy | 1 | | |
| Hemorrhage in pleural cavity | 1 | | |
| Serous pleural effusion | 1 | | |
| Additional diagnoses | | | |
| Fibrous pleural adhesions | 13 | 1 | |
| Healed tuberculous foci | 6 | | |
| Organizing tuberculous pleurisy | 1 | | |
| Tuberculosis of hilar lymph nodes | 2 | 2 | |
| Ascaris in pleura | 1 | | |

* Six of these patients had severe ulcerative enteritis and five others had necrotizing tonsillitis to account for death.

tissues. The parenchyma showed large foci of necrosis which were centered upon the bronchioles, whose lumina were filled with finely granular, pink-staining material containing large clumps of bacteria (Fig. 22). The lining membranes of these bronchioles had become completely necrotic save that portions of the basement membrane persisted. In the vicinity of these bronchioles the shadowy remnants of the walls of the alveoli could still be discerned, but in some places these had become invisible. The alveoli were filled with fibrin, ensnaring large numbers of erythrocytes. No polymorphonuclear leukocytes were found, although large mononuclear elements with phagocytized, finely granular, brown pigment were scattered throughout the tissue.

In some instances the alveoli contained much extravasated blood (Fig. 23), but in others there were relatively few erythrocytes, but relatively much amorphous acidophilic substance, and fibrin was abundant (Fig. 24).

The lungs of 5 patients who presumably had been exposed to radiation exhibited a focal necrotizing pneumonitis in which polymorphonuclear cells were abundant. In these patients the bone marrow was found not to be hypoplastic.

Two patients had a focal caseous tuberculous pneumonitis. It is interesting that the exudate in these lungs contained numerous large mononuclear cells, although polymorphonuclear leukocytes were absent.

The caseous foci were surrounded by large extravasations of blood. Tuberculous foci in other irradiated patients of this group remained quiescent (Table XVIII).

*Spleen (Table XIX).* Usually the malpighian corpuscles remained in a state of atrophy which sometimes was extreme and which might possess all of the features manifest in group I, as late as the 18th day after irradiation (Fig. 42). Atypical large mononuclear cells, such as have been described, frequently were found in large numbers (Fig. 43). In some spleens there were evidences of regeneration (Figs. 41, 45, 46, and 47). The regeneration was of a remarkable type. It appeared at first to be associated with condensation of syncytial spindle-shaped reticulum cells upon the almost naked central arterioles of the malpighian corpuscles. Occasional mitotic figures were found among these reticulum cells. Small lymphocytes were seen in close association with them and indeed seemed to be derived from them. The lymphocytes appeared first between the syncytium and the central arteriole, but also in a halo

TABLE XIX

*Hiroshima, Group II: Spleen*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Histologic specimens available | 51 | 5 | 2 |
| Perisplenic adhesions | 4 | | |
| Decrease of lymphocytes | 48 | 3 | 1 |
| Absence of germinal centers | 49 | | |
| Atypical mononuclear cells | 13 | 2 | 2 |
| Heavy plasma cell infiltration | 7 | | |
| Regeneration with perifollicular condensation of reticulum | 8 | | |
| Infarct | | 1 | |

about the former. Their number increased centrally and it appeared for a time as if the "germinal center" was at the periphery of the follicle. In larger follicles, presumably later in regeneration, minute germinal centers reappeared in their central positions within the follicle.

A morphologically similar "hematopoietic perifollicular envelope" recently has been described in the spleen of the rat by Krumbhaar.[48] In the human spleen only lymphocytes appear to be derived from such cells, while in the rat they may also be precursors of normoblasts and granulocytes.

*Lymph Nodes (Table XX).* Between the end of the second and sixth weeks, there was usually a continued absence not only of the germinal centers of lymph nodes, but also of typical small lymphocytes. The tendency toward shrinkage on this account was counteracted by pro-

TABLE XX

*Hiroshima, Group II: Lymph Nodes*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Microscopic specimens available | 39 | 2 | 1 |
| Marked enlargement of nodes | 2* | 2 | 1 |
| Large nodes composed of typical lymphocytes, but without germinal centers | 1 | | |
| Decrease of lymphocytes | 36 | | |
| Absence of germinal centers | 36 | | |
| Germinal centers present | 2 | | |
| Atypical mononuclear cells | 25 | 1 | 1 |
| Bacterial masses in node, with necrosis | 2 | | |
| Additional observations | | | |
| Tuberculosis | 2 | | |

* K-22 and K-23.

liferation of atypical cells. In 5 instances this proliferative process was so extensive as to produce nodes of several times the usual size. Thus the bare reticular skeleton found in some of the earlier cases only rarely persisted as long as 2 weeks (Fig. 33). On the contrary, the node supported great numbers of atypical large cells, some resembling lymphoblasts (Figs. 49 and 50), some with plasmacytoid characteristics, and others representing very bizarre polymorphous derivatives of the reticulum (Figs. 51 and 52), occasionally with the structure of Reed-Sternberg cells (Fig. 53). Forms intermediate between these and ordinary reticulum cells were common. The inception of this proliferative activity was noted during the first 2 weeks, but now had reached its acme. In Giemsa-stained preparations numerous eosinophils and many mast cells of variable size and shape were present (Fig. 33). Some of the latter were remarkably elongated.

*Bone Marrow (Table XXI).* The tissue available is unique, since relatively little has been published concerning the effects upon the bone marrow in man of single massive doses of ionizing radiations to the whole body. Despite the devastation of the hemopoietic tissues that may occur soon after irradiation, the marrow in later weeks displayed a remarkable regenerative capacity. At first, as in the spleen and lymph nodes, the proliferative activity resulted in the production of atypical cells only. Most marrows in group II patients were of this type. In some marrows there was evidence of direct transformation of reticulum cells into myelocytes (basophilic blast cells being minimal in number), as well as into plasma cells or lymphocytoid elements as described by Rohr.[75] Some marrows, however, especially in patients dying in the fifth and sixth weeks, showed moderate or even extreme myeloid hyperplasia,

TABLE XXI

*Hiroshima, Group II: Bone Marrow*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Long bones | | | |
| Histologic specimens available | 27 | 2 | 0 |
| Type A: hypoplasia | 18 | 1 | |
| Type B: marked focal reticulum hyperplasia | 3 | | |
| Type C: focal myeloid regeneration | 5 | | |
| Type D: marked myeloid hyperplasia | 1 | 1 | |
| Flat bones | | | |
| Histologic specimens available | 22 | 3 | 1 |
| Type A: hypoplasia | 6 | 2 | 1 |
| Type B: marked focal reticulum hyperplasia | 5 | | |
| Type C: focal myeloid regeneration | 10 | | |
| Type D: marked myeloid hyperplasia | 1 | 1 | |
| No marrow | | | |
| Tissue response "aplastic" | 5 | | |
| Polymorphonuclear cells in tissue | 2 | | 1 |

but even in such instances there might be evidence of a "maturation defect," with persistence of peripheral counts below 2000. The marrow of the long bones took part in the regenerative process.

The marrows of group II may be classified according to the degree and type of regeneration as follows:

Type A. Marrows showing marked hypoplasia

Type B. Marrows showing marked focal reticulum hyperplasia

Type C. Marrows showing focal myeloid regeneration

Type D. Marrows showing myeloid hyperplasia

The available material consisted of sections of tissue from either a long or flat bone, in many instances supplemented by smears made from the bones post mortem and stained by the Giemsa or Wright-Giemsa methods. If a flat bone was available, the case was classified according to the histologic features of that bone. If only material from a long bone was at hand, the case was classified according to its histologic appearance but additional information, derived from examination of supplementary smears from the rib, sternum, or vertebra, was applied when it was available.

In 8 of the patients of group II, neither marrow tissue nor smears were available. In those cases, foci of necrosis in the lung, intestine, or skin were examined to determine whether polymorphonuclear leukocytes were present. It will be recalled that even hyperplastic marrow may deliver remarkably few polymorphonuclear cells to the tissue.

The numbers in the various categories are shown in Table XXI. They will now be discussed in turn.

Type A. Some marrows still retained the almost totally aplastic character exhibited by many in the first stage, with only minimal evidence of the proliferation of reticulum and of the formation of varying numbers of plasmacytoid and lymphoid cells. This change was observed even in the ribs, sternum, and vertebrae (Figs. 55 and 56). Grossly, such a hypoplastic marrow had a gelatinous, extremely translucent, pale red appearance, and the bone yielded only a slightly cloudy, almost serous fluid upon scraping or squeezing, in contrast to the abundant, pasty, gray-red material that usually is obtained.

In some instances, with further proliferation, the reticulum and its derivatives began to form thin septa of proliferating tissues among the fat cells. Some of the reticulum cells tended to become round and to be divorced from their fellows while the nuclear membrane became thicker and knots of chromatin became more prominent in some of the larger cells. The chromatin tended to clump at the periphery and all transitional stages could be demonstrated between such elements and the typical ovoid plasma cells on the one hand and the reticulum cells on the other (Fig. 61). Rarely, and to a slight extent, there was differentiation also into myeloid elements. In most of the aplastic cases the megakaryocytes had almost completely disappeared or they might be represented by small stellate elements with vesicular nuclei and faintly acidophilic or neutrophilic cytoplasm about which fibrin tended to be deposited (Fig. 73). Islets of erythropoiesis often persisted despite extreme atrophy of the remainder of the tissue (Fig. 60). In some instances, even they had all but disappeared (Fig. 56). Clinically, these patients all had a profound leukopenia and a moderate or severe anemia.

Type B. In another type, which differs only quantitatively from that just described, there was a striking focal hyperplasia of the reticulum, and the derivative plasma cells and lymphocytoid elements might be prominent in the cellular population. There also was evidence in some instances of differentiation into myeloid cells. In part the marrow was hypoplastic, but elsewhere, particularly near the trabeculae of bone, there had occurred a tremendous proliferation of large stellate cells, whose nuclei varied somewhat in structure (Figs. 62 to 64). Many were large and ovoid, with thin nuclear membranes and delicately reticular chromatin. Others had somewhat thicker nuclear membranes and more prominent knots of chromatin. Despite the stellate shape of the associated cytoplasm, these resembled the nuclei of plasma cells, and there also were large rounded cells whose general structure was plasmacytoid and

some that resembled lymphocytes more than plasma cells. A few cells with scanty basophilic cytoplasm, thick nuclear membranes, and prominent nucleoli, which were thought to be blast cells, also were present. In Giemsa-stained smear preparations some cells were found to contain the fine azurophilic granules of undifferentiated myelocytes. Metamyelocytes were extremely rare. Evidence for the origin of the myelocytes from the stellate cells of the reticulum was the presence of cells transitional between the two, which contained a few of the azurophilic granules (Figs. 36 and 65). There were a few mast cells with numerous prominent basophilic granules closely resembling those of the lymph nodes. A few small islands of erythropoietic tissue also were found. There were also some large and small cells with complexly folded nuclei (Fig. 64). Their cytoplasm was still faintly basophilic and their structure suggested that of megakaryocytes, but some of the smaller cells were intermediate in appearance between megakaryocytes and reticulum cells.

Bacteria were found in 2 cases: streptococci in one (Fig. 66) and thin elongated bacilli in the other (Figs. 67 and 68). Both marrows were well fixed immediately post mortem. In the latter there was necrosis of the tissue, but there was no special leukocytic infiltration about the organisms in either instance. These cases demonstrate the occurrence of bacteremia, which probably was common terminally.

The tremendous focal hyperplasia of reticulum cells may suggest the appearance of "reticulo-endotheliosis" or leukemia. In that instance, involvement of the lymph nodes or other tissues rich in reticulum cells would be expected. In all cases in which "type B" marrow was encountered, however, the Kupffer cells of the liver showed little more than a moderate degree of erythrophagia and hemosiderosis, and there was no unusual proliferation of these cells. In one case with type B marrow, K-22, some of the nodes were markedly enlarged and contained numerous atypical mononuclear and reticular cells. These, however, did not differ from the atypical cells of the spleens and nodes of many other patients in whom the bone marrow was notably hypoplastic. Unfortunately, no leukocyte counts are available for K-22, but there appeared to be some differentiation of the reticulum into myeloid tissue, despite the rarity of the blast cells. It seems preferable to regard this proliferated reticulum merely as hyperplastic tissue, little differentiated, but without obvious neoplastic properties.

A single case of leukemia of monocytic type occurred among the approximately 14,000 patients studied clinically in the two cities. This case is presented in group III.

Type C. In a third type, myeloid tissue definitely predominated in

small foci where regeneration was in progress. In these foci there might still be evidence of proliferated reticulum, and excessive numbers of plasma cells and lymphocytes still were present. Myeloid hyperplasia in this instance was focal, and there was maturation at least into metamyelocytes. Megakaryocytes appeared in increasing numbers. There was no sharp separation between the marrows of this type and those of type A or B.

Occasionally, in the Nagasaki series, eosinophils, mature and immature, were prominent in such marrows, particularly in group III (patients dying after the sixth week).

Type D. In the fourth type, seen rarely in this group, hyperplasia was extreme and the fat cells were hardly visible amid the masses of myelocytes, and in some instances metamyelocytes. The cytologic characteristics of this marrow did not differ essentially from that of type C, except for predominance of the more mature cells.

The last two types became predominant after the sixth week, and will be described and illustrated in group III.

Comparison of Tissue from Various Bones. Cell counts of bone marrow smears made at autopsy are summarized in Table XXII and in Text-Figure 1. They are grouped according to classification of histologic specimens. Thus, by reading the chart horizontally, the cytologic features of the various bones in a particular type of case can readily be compared. The columns read vertically show variations in the counts for any particular bone from case to case.

A common feature was the great increase in the reticular and lymphoid tissue, largely at the expense of the myeloid tissue. The erythroid tissue also had suffered decrease but the reduction was less in comparison with normal values.

The femur took part in the regenerative process along with the flat bones, and in some instances hyperplasia, reticular or otherwise, in the femur was extreme. Usually the smears from the flat bones conformed to the histologic structure of the long bones; in some instances there was relatively more myeloid tissue in the former. Even from long bones, however, smears showed the same contrast with fixed tissue, probably because the free, more differentiated cells are yielded more readily to the glass than are the reticular elements.

Of all flat bones, the sternum showed the earliest regeneration and the greatest cellularity, but occasionally even the femur exceeded the sternum in these respects.

TABLE XXII

*Hiroshima, Group II*: Comparison of Fixed Tissues and Post-Mortem Smears of Bone Marrow*

| Cell type | Source and differential count† of smear: Sternum | Rib | Vertebra | Femur | Histology of fixed tissue |
|---|---|---|---|---|---|
| M | 12.0 | 6.6 | | | |
| L | 31.5 | 43.5 | | | Femur, type A marrow |
| R | 53.1 | 45.8 | | | |
| E | 3.4 (Average of K-26, 27, 31) | 4.1 (Average of K-21, 24, 25) | | | |
| M | 6.0 | | | 18.0 | |
| L | 29.0 | | | 30.0 | Femur, type A marrow (K-30) |
| R | 60.0 | | | 48.4 | |
| E | 5.0 | | | 3.6 | |
| M | 21.6 | | 7.0 | 7.0 | |
| L | 33.6 | | 49.0 | 49.0 | Sternum, type A marrow (K-42) |
| R | 28.8 | | 34.0 | 34.0 | |
| E | 16.0 | | 10.0 | 10.0 | |
| M | | 21.1 | | 32.2 | |
| L | | 44.0 | | 38.2 | Vertebra, type A marrow (K-37) |
| R | | 32.8 | | 28.6 | |
| E | | 2.1 | | 1.0 | |
| M | | 24.8 | | | |
| L | | 30.5 | | | Femur, type B marrow |
| R | | 31.7 | | | |
| E | | 13.0 (Average of K-29, 44) | | | |
| M | | | 51.5 | | |
| L | | | 13.5 | | Vertebra, type B marrow (K-22) |
| R | | | 27.0 | | |
| E | | | 8.0 | | |
| M | 5.0 | | | 19.0 | |
| L | 35.0 | | | 35.0 | Sternum, type B marrow (K-43) |
| R | 55.0 | | | 42.0 | |
| E | 4.0 | | | 4.0 | |
| M | 29.3 | | | | |
| L | 21.6 | | | | Femur, type C marrow (K-32) |
| R | 43.1 | | | | |
| E | 5.0 | | | | |

* This series of specimens is derived from patients dying during the third and fourth weeks.

† Counted by Dr. G. V. LeRoy.

Key: M = myeloid cells; L = lymphoid cells; R = reticular cells (reticulum and plasma cells, and intermediate forms); E = erythroid cells. Types A, B, and C marrows are defined in text.

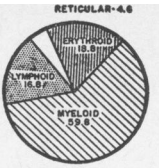
In drawing conclusions from this material, both from histologic and smear preparations, it must be remembered that one is dealing with very small and possibly unrepresentative portions of the entire vast body of the marrow.

# HIROSHIMA

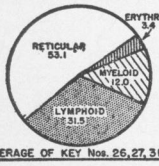
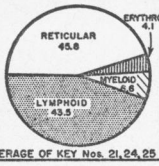
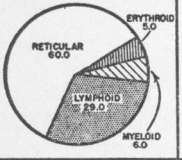
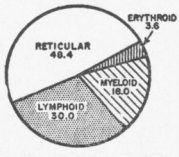
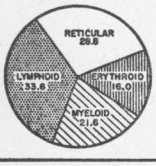
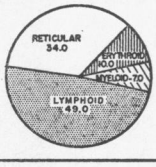
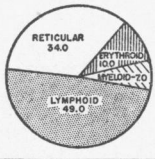
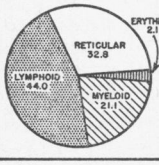
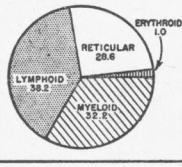
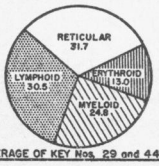
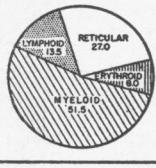
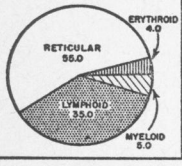
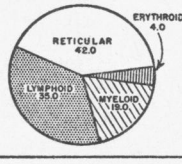
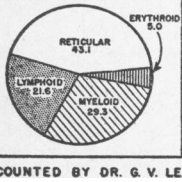
## COMPARISON OF FIXED TISSUES AND SMEARS OF BONE MARROW

### GROUP II

(Patients dying during 3rd. & 4th. week)



NORMAL

| SOURCE, & DIFFERENTIAL COUNT* OF SMEAR | | | | HISTOLOGY of FIXED TISSUE |
|---|---|---|---|---|
| Sternum | Rib | Vertebra | Femur | |
|   AVERAGE OF KEY Nos. 26, 27, 31 |   AVERAGE OF KEY Nos. 21, 24, 25 | | | Femur Type A |
|   | | |   | Femur Type A (KEY No. 30) |
|   | |   |   | Sternum Type A (KEY No. 42) |
| |   | |   | Vertebra Type A (KEY No. 37) |
| |   AVERAGE OF KEY Nos. 29 and 44 | | | Femur Type B |
| | |   | | Vertebra Type B (KEY No. 22) |
|   | | |   | Sternum Type B (KEY No. 43) |
|   | | | | Femur Type C (KEY No 32) |

* COUNTED BY DR. G. V. LE ROY

Text-Figure 1

Relation of Leukocyte Counts to the Histologic Structure of the Marrow. Reference to Table XVI will show that in all but one of the 34 patients in group II for whom leukocyte counts have been recorded, the count had been 2500 or less at some time before death and in most of these patients it was below 1000. This leukopenia had no relation to the type of marrow ultimately found at necropsy.

Maturation Defects. In certain instances, there was striking evidence of maturation defect, for, despite diffuse myeloid hyperplasia, peripheral counts sometimes remained remarkably low. The history of K-108 is detailed as an example.

The patient was a 29-year-old man, who was at a distance of 700 yds. from the hypocenter. He was outdoors a few paces from a concrete building. He was struck by fragments of a falling roof which inflicted slight injuries to the head and neck. There was nausea on August 6 (the day of the bombing), and on the same day he vomited between 20 and 30 times. Malaise began on August 6 and lasted until the 10th, accompanied by anorexia. He again experienced malaise beginning on August 21 until the time of death. Anorexia appeared 4 days after the second onset of malaise. There was epilation, and gingivitis on August 21, which persisted. The gingivae began to bleed on August 30. On the 25th purpuric manifestations began and there was evidence of tonsillitis, both symptoms lasting until death on September 1. There was high fever between August 24 and the time of death, and there was cough and sputum beginning on the 25th, with hemoptysis on August 30.

| | Red blood cells | White blood cells |
|---|---|---|
| August 24 | 3.95 millions | 370 |
| August 26 | 5.64 millions | 450 |
| August 29 | 4.19 millions | 200 |
| August 30 | | 220 |

The urine examined on August 29 was positive for albumin and negative for sugar. No statement was made concerning sediment.

The marrow of the patient, in sections derived apparently from the cavity of a long bone, was of type D, showing vascular adipose tissue crowded by very large numbers of young myelocytes. Mature polymorphonuclear leukocytes and even band cells were rare. There was an occasional megakaryocyte. Occasional cells were found in mitosis. A few small nests of shrunken nuclei, thought to be those of normoblasts, also were found. Other significant lesions at necropsy were petechiae of the skin, epilation of scalp, focal necrosis of pharynx, tongue, tonsils, and larynx, necrotizing gingivitis, an abscess in the region of the right mandibular joint, necrotizing and hemorrhagic neutropenic pneumonia, and minute hemorrhages of the gastro-intestinal tract, trachea, and renal pelves.

Rising Counts. Occasionally, however, patients who had had a profound leukopenia manifested a rise in count to approximately 5000, before death. This is demonstrated in K-86 (sub-group 211).

At the time of the bombing, the patient, an 18-year-old girl, was at home in bed at Kawaramachi, approximately 800 yds. from the hypocenter. She was injured by fragments of glass which entered both upper extremities, the left submaxillary region, the back, and the left knee joint. She lost consciousness for a time. The wounds progressed favorably, but on August 20 she noted epilation and suffered diarrhea. Suddenly in the night of August 30 there was high fever, accompanied by severe sore

throat. She was admitted to Iwakuni Naval Hospital on August 31, 1945. On that date the white blood cells numbered 960 per cmm.; on the next day, 620; then they fell daily to a minimum of 100 on September 5, 1945. After that the count gradually increased to 480, 1680, 3200, and 7980. Her general condition, however, worsened and she died on September 9.

At necropsy the bone marrow showed a moderate focal hyperplasia with myeloid differentiation (type C). The other findings included epilation of scalp, scattered petechiae of the viscera, atrophy of the lymphoid tissue, and a necrotizing focal pneumonia.

A rising leukocyte count is much more frequently recorded in patients dying later (group III). Obviously, moreover, many patients, in whom the marrow, after a period of depression, became capable of producing a leukocytosis, recovered and escaped inclusion in the autopsy series.

*Gastro-intestinal Tract (Table XXIII).* Hemorrhages and ulceration occurred very frequently in the gastro-intestinal tract in patients dying

TABLE XXIII

*Hiroshima, Group II: Gastro-intestinal Tract*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Stomach | | | |
| Gross specimens available | 58 | 5 | 2 |
| Petechiae | 36 | 2 | |
| Diffuse necrosis and hemorrhage | 1 | | |
| Ulcers and hemorrhages | 4 | | |
| Plasma cell infiltration | 1 | | |
| Small intestine | | | |
| Gross specimens available | 58 | 5 | 2 |
| Petechiae | 19 | | |
| Ulcers and hemorrhages | 7 | | |
| Large intestine | | | |
| Gross specimens available | 58 | 5 | 2 |
| Petechiae | 14 | | |
| Ulcers and hemorrhages | 26 | | 1 |
| Additional diagnoses | | | |
| Ascariasis | 16 | 1 | |
| Chronic ulcer of pylorus | 1 | | |
| Perforation (agonal) of cardia | 1 | | |
| Scars of ileum | 1 | | |
| Absence of appendix | 1 | | |

between the third and seventh weeks. The tissue response usually was neutropenic. In their pathogenesis these lesions probably represented the results of infection associated with the aplastic anemia, perhaps initiated in some cases by the direct action of the ionizing radiations upon the epithelium. Beyond the second week, however, the atypical epithelial cells found earlier were no longer in evidence.

Petechiae almost always were present in the stomach. They were most numerous in the vicinity of the magenstrasse, but occurred also elsewhere in the mucous membrane. Ulcerative lesions occurred occa-

sionally in the stomach, and the tissues at the base and margins of the ulcers were suffused with blood. At times necrosis and hemorrhage were diffuse, with great swelling and induration of the mucous membrane (Fig. 84). The surface assumed a dull gray-green, lusterless appearance which bordered sharply upon typical pale-pink mucous membrane. The necrotic material was underlain by a strikingly edematous and hemorrhagic mucosa. Histologically, almost no polymorphonuclear cells were found (Fig. 89) but there were numerous plasma cells in the lamina propria. Among these there were also spindle-shaped elements with nuclei resembling those of the plasma cells but with elongated bodies of cytoplasm like those of fibroblasts. Near the mouths of the glands many of the epithelial cells were found in mitosis. Most of these were in metaphase and did not appear to be atypical. At the very surface in some places there was necrosis and hemorrhage which extended halfway to the muscularis mucosae. Purple-staining bacterial masses existed in the superficial portions of the necrotic material, but no leukocytic barrier delimited the latter. The submucosa was greatly thickened by edema, and there were present large stellate elements, fibroblasts, macrophages, and mast cells. The bundles of the muscularis also were widely separated by edematous connective tissue. Irregular hemorrhages were present within the submucosa also and there were scattered lymphocytes, plasma cells, and rare eosinophils in the superficial portions of this tissue near the muscularis mucosae.

In the small intestine also there were foci of necrosis, usually discrete. They were most numerous in the region of the ileocecal valve where there was almost always involvement (Figs. 85 to 87).

In the large intestine, which was most frequently involved, the necrosis might be diffuse (Fig. 88) but the lesions usually were focal. Often there was a polypoid projection of edematous hemorrhagic tissue into the lumen of the bowel rather than an ulcer crater. The projecting mass was covered by an opaque, ashen, yellow or gray-green material, and at its base there was a halo of hemorrhage. Histologically, the tissue response again was usually aplastic (Fig. 91) or largely of the plasma cell type (Fig. 90).

Only in 4 instances were large numbers of polymorphonuclear leukocytes found in the exudate at the base of the intestinal ulcers. Most of these patients died toward the end of the fifth and during the sixth week, when the marrow was experiencing a measure of return of myelopoiesis.

*Liver (Table XXIV).* Contrary to the gross descriptions of the Japanese pathologists, fatty change was rarely encountered in the liver

TABLE XXIV

*Hiroshima, Group II: Liver and Gallbladder*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Histologic specimens available | 55 | 4 | 1 |
| Perihepatic fibrous adhesions | 3 | | |
| Subcapsular hemorrhage | 1 | | |
| Giant nuclei in pericentral hepatic cells | 4 | | |
| Central congestion | 24 | 2 | |
| Edema of pericentral connective tissue | 8 | 1 | |
| Edema of periportal connective tissue | 2 | | |
| Focal fatty changes: Periportal | 1 | 2 | |
| Midzonal | 1 | | |
| Irregular | 1 | | |
| Focal necrosis: Periportal | 1 | | |
| Pericentral | 1 | | |
| Pylephlebitis | 1 | | |
| "Hyaline bodies" in cytoplasm | 1 | | |
| Gallbladder | | | |
| Petechiae | 1 | | |
| Additional diagnosis | | | |
| Hepatoma | 1 | | |

in this stage. It was observed microscopically in but 5 cases. Necrosis also was rare and was observed only once in pericentral and once in periportal positions. When present, the lesions were widely disseminated. The cellular exudate was scanty, had itself largely become necrotic, and consisted for the most part of plasma cells (Fig. 94). In one instance some of the large intrahepatic portal veins were involved in pylephlebitis. There was no evidence of ascariasis in that case, but there were focal necrotizing lesions of the intestine, which may well have been the source of the bacterial infection that probably was concerned in the pathogenesis of the hepatic lesions.

Slight central congestion again was frequently observed, as in group I, and there was occasionally thickening of the walls of the central veins, presumably edematous. Large nuclei were observed also in hepatic cells at the central ends of the cords.

*Pancreas.* No significant changes were observed in any pancreas seen grossly nor in the 25 that were inspected microscopically.

*Kidney (Table XXV).* Perirenal and pelvic hemorrhages were extremely common in patients dying during the second 4 weeks. Histologically, these consisted merely of erythrocytes infiltrating loose connective tissue in the capsule, and beneath the epithelium of the pelvis, without admixture of other cells. Occasionally the pelvic hemorrhages were diffuse (Fig. 97), and in some instances the ureter and bladder were involved also.

TABLE XXV
*Hiroshima, Group II: Kidney*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Specimens available | 56 | 5 | 0 |
| Hemorrhages of pelvis | 33 | 4 | |
| Cloudy swelling | 13 | 1 | |
| Glomerular hemorrhages | 6 | | |
| Hemorrhages in pyramid | 1 | 1 | |
| Hemorrhagic pyelonephritis | 1 | | |
| Scars of kidney | 17 | | |
| Abscesses (with polymorphonuclear cells) | | 1 | |
| Atypical large mononuclear cells in sinusoids | 1 | | |
| Additional diagnoses | | | |
| Leiomyomata of pyramids | 1 | | |
| Double pelvis and ureter | 1 | | |

Glomerular hemorrhages (Fig. 97) were demonstrated in approximately 10 per cent of the kidneys of patients dying during this period. Grossly, such kidneys had the "flea-bitten" appearance found in acute glomerular nephritis. The nephrons in these cases, however, merely showed hemorrhages in the subcapsular spaces and tubules, without notable proliferative changes in the glomeruli. Often a few minute scars were found, within and about which plasma cells and occasional large mononuclear cells represented the only elements of a cellular exudate. There was often cloudy swelling of the elements of the proximal convoluted tubules which, in association with anemia, accounted for the pale appearance of most of these kidneys. In one instance there was hemorrhagic pyelonephritis associated with hemorrhage and necrosis in the prostate. A few polymorphonuclear leukocytes were found in the kidney in this instance.

The large and small mononuclear cells, so prominent in the medullary sinusoids in the kidneys of patients of group I, occurred only once in the group II series.

*Ureters and Bladder.* In 4 instances focal hemorrhages were found beneath the mucous membrane of the ureters. Such lesions also occurred in the bladder in 3 instances, in another the process was diffuse, and in a fifth there was diffuse hemorrhage associated with an acute necrotizing cystitis.

*Prostate and Seminal Vesicles.* The necrotizing hemorrhagic lesion of the prostate in the patient with necrotizing pyelonephritis has already been mentioned. A few leukocytes, chiefly unsegmented polymorphonuclear cells, were present within the bladder, but they were very rare in the kidney.

The seminal vesicles showed no changes except that in one instance the contents were noted histologically to be an acidophilic material containing almost no spermatozoa.

*Testes (Table XXVI).* In all 38 of the available specimens in this group of 52 male patients there was atrophy of the testicular substance.

TABLE XXVI

*Hiroshima, Group II: Testes*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Well nourished patients | | | |
| Histologic specimens available | 25 | 1 | 0 |
| Atrophy of germinal epithelium and derivatives | 25 | 1 | |
| Thickening of basement membranes of tubules | 4 | 1 | |
| Hyaline changes of blood vessels | 7 | | |
| Hyperplasia of interstitial tissue | 2 | | |
| Malnourished patients | | | |
| Histologic specimens available | 11 | 0 | 1 |
| Atrophy of germinal epithelium and derivatives | 11 | | 1 |
| Thickening of basement membrane of tubules | 4 | | |
| Hyaline changes of blood vessels | 1 | | |
| Hyperplasia of interstitial tissue | 1 | | |
| Hemorrhage of tunica albuginea | 1 | | |

Since the effect of inanition* is well known, an attempt was made to determine from the records whether the patients were well nourished. Inanition usually was recorded by the Japanese pathologists or could be determined, when severe, by inspecting the subepicardial, subcutaneous, or perirenal adipose tissue in histologic sections. Twelve patients were considered to be slightly or severely malnourished; the other 26 were apparently in a good state of nutrition at the time of death. The changes to be described must also be considered in the light of the fact that some degree of testicular atrophy is common in many exhausting illnesses. In these illnesses, however, it is rarely as complete as that observed here. Most of the irradiated patients had only a short bout of high fever before death, so that this could hardly be considered a factor in the atrophy of the testes, and none had generalized lesions suggestive of typhus. Allen and Spitz[2] described testes in their scrub typhus patients that resemble those illustrated here.

Clinical sperm counts performed some 10 weeks after irradiation on survivors who were well nourished, epilated, but apparently otherwise well, showed a close correlation between the degree of exposure as judged by distance from the bomb and the degree of hypospermia. This is con-

* Testes of patients from the German prison camp at Dachau studied by Capt. E. B. Wert at the Army Institute of Pathology show all the changes described in this section. These patients weighed approximately 80 lbs. at the time of death.

firmatory evidence that the testicular changes represented at least in part an effect of radiation.

Only in one case was there a notable gross reduction in the size of the testes (Fig. 99). The masses of tubules appeared pale gray-tan but strung easily from the cut surface. Histologically, all of these testes showed separation of most or all of the germinal epithelium from the basement membrane, which was then lined by a continuous layer of tall Sertoli cells. Partly necrotic remnants of germinal epithelium and its derivatives were seen in the lumina of the tubules (Figs. 100 and 101). Spermatids and spermatozoa, however, sometimes remained embedded among the Sertoli cells. Occasionally there was found, near the basement membrane or in the lumen, a large ovoid cell with a densely reticular nucleus which from its structure was thought to be a relic of a germinal epithelial cell (Fig. 102).

Occasionally there occurred in the lumina of the tubules what appeared to be multinucleated giant cells. These apparently were formed by fusion of the cytoplasm of remnants of spermatids, successive stages of which are shown in Figures 103 and 104. Such a fused mass might become moulded into a rounded shape somewhat in the manner of a corpus amylaceum. The nuclei of such "giant cells" had a dull, homogeneous, non-reticular structure unlike that of viable cells. Barratt and Arnold[8] considered such cells in the testis of the rat after x-irradiation to be the result of atypical mitosis or amitosis of spermatocytes.

The basement membranes of the tubules within the first 5 or 6 weeks usually remained thin, but were found to be slightly thickened in a few instances (Fig. 104). In one malnourished boy of 8 years there was a remarkable thickening of the basement membrane of the tubules of the immature testes (Fig. 106). The epithelium appeared only slightly shrunken. The fate of other heavily irradiated young patients will be of great interest.

The small blood vessels of the interstitium sometimes showed deposits of a refractile acidophilic material beneath the apparently intact endothelium, with considerable restriction of the lumen (Fig. 100).

Even before there was a marked shrinkage of the tubules there might be a suggestive increase in the interstitial cells of Leydig not resulting from compaction of the tissue. This occurred uncommonly but is evident in Figure 101. It is apparently the result of hyperplasia of the Leydig cells rather than of compaction.

Changes in the hypophysis, presumably associated with the lesions in the testes, will be discussed later in this report.

*Ovaries and Uterus (Table XXVII).* Little suitable material from ovaries and uterus was available for inspection. There were sections of the ovaries from 10 of the 12 female patients in group II. Of these, 3 were of postmenopausal and 2 of premenstrual age. The latter usually showed numerous undeveloped follicles, some in process of atresia. In

TABLE XXVII

*Hiroshima, Group II: Ovaries and Uterus*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Ovaries | | | |
| Histologic specimens available | 10 | 0 | 0 |
| Postmenopausal | 3 | | |
| Pre-menarche | 2 | | |
| Ova and corpora albicantia present, developing follicles absent | 4 | | |
| Marked atresia of follicles* | 1 | | |
| Corpus luteum of pregnancy | 1 | | |
| Uterus | | | |
| Histologic specimens available | 6 | 0 | 0 |
| Endometrium in resting phase* | 3 | | |
| Postmenopausal | 2 | | |
| Decidual reaction, following pregnancy | 1 | | |

* In sexually mature women.

the former there was complete involution. The four ovaries from non-pregnant women in the functional age group had in common the presence of corpora albicantia and primordial follicles without developing follicles or corpora lutea. In one young woman the primary follicles were remarkably few and those that remained were in process of atresia (Fig. 109). In some instances the ova had become shrunken in this case (Fig. 111) and granulosa cells compacted in a group at the center of the follicle. Subendothelial acidophilic deposits restricted the lumina of some vessels of the ovary as of the testis (Fig. 112).

The endometrium in all of these cases was in the "resting phase" and the central glands were lined by columnar epithelium that showed no evidence of corpus luteum effect. The spindle-shaped cells of the endometrial stroma were thin, small, and elongated.

One pregnant patient, 38 years of age (K-61) who had been in a Japanese building at 1100 yds. and who had subsequently become epilated, died on the 35th day apparently of ulcerative enteritis, shortly after she had aborted a 5 months' fetus. A corpus luteum of pregnancy was found in an ovary and there were still fragments of decidual tissue in the uterus. The resistance of the corpus luteum of pregnancy to irradiation is well known.

Neither the uterus nor its appendages escaped the hemorrhages that

involved the other tissues. They occurred in the endometrium or serosa of the uterus, the ovaries, and fallopian tubes (Fig. 108).

*Brain (Table XXVIII).* Congestion of the leptomeninges and intracerebral vessels usually was in evidence. In one instance there were large subpial, or multiple punctate subependymal hemorrhages (Fig. 113).

TABLE XXVIII
*Hiroshima, Group II: Brain*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Gross specimens available | 37 | 0 | 0 |
| Histologic specimens available | 7 | 0 | 0 |
| Subpial hemorrhages | 5 | | |
| Subependymal petechiae | 1 | | |
| Petechiae of cerebral substance | 1 | | |
| Ecchymosis of dura | 1 | | |
| Epidural hematoma | 1 | | |
| Focal hemorrhage and necrosis | 1 | | |

Petechiae or ring hemorrhages were found also in several sites, including the corpus callosum, within the same brain. In another patient masses of bacteria were found within necrotic tissue surrounded by hemorrhage (Fig. 114). About these there was no leukocytic response.

There was evidence of former trauma in one epidural hematoma, but most of the hemorrhagic lesions probably had the same pathogenesis as those of the other organs.

The ganglion cells in general were well preserved, except in the vicinity of foci of hemorrhage or necrosis.

*Adrenals (Table XXIX).* The adrenals were almost always remarkable for their small size, which bore no apparent relation to the nutri-

TABLE XXIX
*Hiroshima, Group II: Adrenals*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Gross specimens available | 58 | 5 | 2 |
| Histologic specimens available | 47 | 4 | 1 |
| Gross evidence of loss of lipoid, no microscopic sections available | 11 | | 1 |
| Atrophy of cortex, especially of the zona glomerulosa | 30 | 2 | |
| Focal necrosis | 1 | 1 | |
| Fibrinous material in periadrenal fat | 3 | | |
| Periadrenal hemorrhages | 8 | 1 | |
| Hemorrhages of cortex | 3 | 1 | |
| Heavy plasma cell infiltration | 1 | | |
| Thrombus in arteriole | | 1 | |

tional state of the patient. The outer cortex usually was remarkably narrow and was composed of translucent yellow-gray, rather than

orange-yellow, opaque tissue. This change usually was diffuse, but might be focal. The cortex at times came to resemble the gray, translucent, medullary substance. In a few instances cortical or periadrenal hemorrhages might be seen but in no instance was there a notable degree of disruption of the organ. Often, in association with the hemorrhage, there had been exudation of protein-containing material or fibrin into the areolar septa of the periadrenal fat.

Microscopically, the cells of all layers usually had finely granular rather than vacuolated cytoplasm, confirming the impression of loss of cortical lipid that was gained from the gross inspection. The cells of the deeper fascicular and reticular layers tended in some measure to retain their vacuolation. In some instances, scattered groups of cells, especially in the zona fasciculata, had extremely foamy cytoplasm and pyknotic, centrally placed nuclei. In one such, there was also focal necrosis with infiltration of large fat-filled phagocytes (Fig. 117). A remarkable finding in the same case was that of numerous mitotic figures in the epithelial cells of the central part of the zona fasciculata (Fig. 118).

Cells resembling plasma cells usually were present in small numbers in the medulla, at the corticomedullary junction, and at times also in the cortex. In one instance these cells were very numerous for no evident reason. There was no indication that they represented erythropoietic or myelopoietic tissues.

No information is available concerning the effects of castration upon the adrenals in man. In male mice, however, an increase in the thickness of the zona reticularis has been observed.[56] The pathogenesis of the adrenal atrophy observed in many of group II patients is unknown.

*Thyroid Gland.* Fifty-four gross and 16 histologic specimens of thyroid tissue were available. The follicles usually were small, lined by low-cuboidal epithelium, and filled with palely staining colloid.

*Thymus.* There were no notable changes in the 3 available specimens of thymus except for hemorrhage in one.

*Pituitary Body.* Twenty hypophyses were available in which the cells were well enough preserved to be recognizable as to type. Four were from female and 16 from male patients. Fixation, however, was imperfect in most of these since the capsule of the gland usually had not been opened before it had been put in the formalin solution.

Large basophilic vacuolated "castration cells" were found in 4 of the 16 male patients. In the instance illustrated in Figure 37, the basophilic cells generally were large and some had huge vesicular nuclei. In many cells vacuoles had formed in the cytoplasm and the basophilic granules were widely scattered within the trabeculae of cytoplasm. Vacuolization

was extreme in some cells which had become gigantic. The basophilic granules in them were few and the nucleus was displaced to one side in "signet ring" fashion. Cells of this type are found in most species of animals following castration.[77]

Some coarsely vacuolated basophils were found also in one female patient who had shortly before aborted a 5 months' fetus. Groups of large "pregnancy cells" were present also in this hypophysis.

In one other male and in one female patient the basophilic cells were thought to be unusually large and numerous although they were not vacuolated. However, it is difficult to draw conclusions from these sections without statistically adequate measurements and counts. Unfortunately, only single slides are available.

An interesting incidental finding in one case (K-38) was the presence of a minute chromophobe adenoma.

It is of interest to note that these changes in the pituitary body took place despite the fact that the Leydig cells remained morphologically intact and were numerous following complete atrophy of the germinal epithelium of the testes.

*Neck and Mouth Organs (Table XXX).* Hemorrhagic and necrotizing lesions of the mouth and neck organs were frequent at this stage,

TABLE XXX

*Hiroshima, Group II: Mouth and Neck Organs*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Gross specimens available | 53 | 5 | 2 |
| Gingivitis, all types | 23 | | |
| Hemorrhagic | 12 | | |
| Necrotizing | 9 | | |
| Type unstated | 2 | | |
| Necrotizing glossitis | 3 | | 1 |
| Necrotizing tonsillitis | 65 | | |
| Faucial | 40 | 1 | 2 |
| Lingual | 25 | | |
| Necrotizing pharyngitis | 13 | | |
| Necrotizing epiglottitis | 21 | | |
| Hemorrhages of epiglottis | 4 | | |
| Edema of epiglottis | 3 | | |
| Necrotizing laryngitis | 7 | | |
| Hemorrhages of larynx | 4 | | |
| Edema of larynx | 2 | | |
| Necrotizing tracheitis | 1 | | |
| Hemorrhage of trachea | | 1 | |
| Ulcerative esophagitis | 2 | | |
| Petechiae of esophagus | 1 | | |
| Leukoplakia of esophagus | 1 | | |

especially in the gums and tonsils. They appeared at a time when leukopenia had made the patients most susceptible to infection. What rôle

such direct radiation effects as have been described in the patients of group I play in their causation is problematic.

The gingivae became greatly swollen and infiltrated with extravasated blood. Their margins became necrotic, often with much sloughing of tissue, so that the alveolar process was exposed. Nevertheless, the teeth remained firmly attached. Pressure released quantities of hemorrhagic material from the periodontal tissues. Healing might occur with a superficial scar, resembling a zone of leukoplakia upon gross inspection. The lips as well as the lining of the mouth might become similarly involved.

Occasionally, the anterior portion of the tongue was the seat of necrosis and hemorrhage (Fig. 124), but these changes were more frequent on the dorsum where they involved the covering epithelium as well as the substance of the subjacent lymphoid follicles (Fig. 123).

More common than lingual was faucial tonsillitis. The tonsils usually were moderately and sometimes greatly enlarged, but on occasion there was no increase in size, despite total necrosis of the organ (Fig. 122). There often was complete necrosis also of tissue elsewhere in the wall of the pharynx, apart from the lymphatic tissue. Such lesions often were outlined by hemorrhagic borders and were seen also in the epiglottis, larynx, and trachea (Fig. 122).

Histologically, these lesions had in common a uniform necrosis with no barrier of polymorphonuclear leukocytes (Fig. 125) although there was a sharp line of demarcation from the relatively intact tissue. Beneath and about the lesion, however, there frequently was edema and sometimes hemorrhage. The cellular exudate, when present, consisted of scattered plasma cells and occasional small and large mononuclear elements (Fig. 126). Often, as in the tonsils, the necrosis involved lymphoid tissue, whose mature lymphocytes, as elsewhere, had almost completely disappeared and in which there was compaction of the reticulum. The reticulum had in many cases differentiated into the large atypical cells that have been described previously. In one case the lesions of thrush were observed (Fig. 127), suggesting the low state of resistance of the patient.

*Skin.* Of 65 patients in group II from whom specimens of skin were available, 58 were noted to have cutaneous hemorrhages at the time of death (Table XXXI). These varied from petechiae (Fig. 128) to large ecchymoses.

Ulcerative lesions of the skin not related to burns also were frequent and several were pustular. An example of an ulcerative lesion of a common type is shown in Figures 129, 131, and 132. As the region of

TABLE XXXI
*Hiroshima, Group II: Skin*

| Observations | Sub-group | | |
|---|---|---|---|
| | 211 | 212 | 222 |
| Gross specimens available | 58 | 5 | 2 |
| Epilation | | | |
| Scalp | 48 | 2 | |
| Axillary | 8 | | |
| Pubic | 6 | | |
| Eyebrows | 4 | 1 | |
| Beard | 2 | | |
| Petechiae or purpura | 53 | 4 | 1 |
| Ulcers | 20 | | |
| Pustules | 3 | | 1 |

denudation of the epithelium was approached, the superficial layers of cells became swollen and frequently the nuclei were found as contracted, deeply staining masses, situated within a clear cytoplasm. The deeper epithelial layers were well preserved and their nuclei were large and finely dotted with chromatin. Pigment also was present within the cells. As the margin of the ulcer was approached, the epithelium became more and more vacuolated and ultimately the nucleus was lost. In some places there was parakeratosis. The base of the ulcer itself consisted of necrotic collagen which was focally infiltrated with numerous erythrocytes. There were no leukocytes except in the septa of areolar tissue that traversed the deeper layers of the subcutaneous fat. These were of small mononuclear and plasma cell types. Even at a distance from the ulcer the skin appendages were surrounded by groups of small mononuclear cells and plasma cells. So also were the vessels of the papillae. In another instance (Fig. 130) exudate was more abundant, but it consisted largely of plasma cells and large mononuclear elements.

The mechanism of origin of the ulcerative lesions is of interest. Whether they were merely the result of infection of the skin in the patients with leukopenia or whether they were in part also the direct result of radiation is difficult to decide. The Japanese described the appearance of "blisters" of the unburned skin of some of the exposed patients. In the records of the necropsies of 2 individuals, K-98 (group I) and K-109 (group II), who were recently dead, the skin was said to have "peeled" easily revealing a pink raw surface beneath. The tongue, pharynx, and esophagus of one of these patients, K-98, showed remarkable changes in the epithelium with sloughing over large areas. This has already been described (Figs. 119 to 121). This patient died on the tenth day after exposure. Unfortunately, skin was not available and there is no supporting evidence for the concept that such ulcerative lesions are direct radiation effects in patients who died at a later date.

The only unburned skin available from most of these patients was the scalp. The changes in the surface epithelium of that region were slight, and in the patients dying later there was no evidence of telangiectatic lesions nor of any remarkable alterations in the collagen.

Epilation appeared in most instances approximately 2 weeks after the irradiation and involved men and women alike. It tended to have the same distribution as ordinary baldness in men, but in some instances the temporal and occipital regions also became epilated. Even then, a few hairs tended to remain (Fig. 9). The beard and eyebrows, and the axillary and pubic hair were relatively resistant to epilation. Regrowth of the hair usually was in progress within 8 weeks after the bombing at Hiroshima and at about 12 weeks at Nagasaki, and the new hair, initially finer, ultimately possessed the same color and texture as the old (Fig. 133).

The changes in the hair follicles are of interest and were illustrated in all phases in heavily radiated patients. If a typical hair follicle is examined (Fig. 134), it will be seen that from the matrix at the root there are differentiated strata of acidophilic trichohyalin-bearing cells (Henle's and Huxley's layers) forming an internal root sheath which is separated along a cuticle from the external root sheath. The latter is an invagination of the epithelium of the surface. Keratinization of the hair begins internally, from the trichohyalin-bearing cells of the internal root sheath very near the base of the follicle. A large keratinized shaft of hair consequently passes through the corium on its way to the surface, separated for much of its course from the external root sheath by a space.

In follicles of the scalp of the irradiated patients, however, the trichohyaline layer failed to differentiate, so that a plug of epithelium resulted which had the structure of, and was continuous with, the external root sheath. Moreover, the pigment was found irregularly distributed throughout the epithelium even at a distance from the papilla (Fig. 135). The epithelium of the matrix became flattened and less basophilic and mitotic figures among its cells became rare, whereas usually they were numerous. The matrix then formed a shallow cap rather than a long hood over the tip of the papilla. The papilla itself became less vascular and smaller and its component elongated spindle-shaped cells were compacted. Often the papilla ceased to be intimately applied to the matrix epithelium and a space appeared between the two tissues. The plug of epithelium at the base of the follicle became more and more narrow, and a whorled, pearl-like arrangement of cells might result (Fig. 136). At the same time both the glassy sheath and the external, more cellular,

fibrous membrane became considerably and often greatly thickened. Spaces appeared beneath the glassy sheath and the shrinking plug of epithelium which had become the core of the follicle. Stains for elastic tissue demonstrated that, despite its wavy refractile character, the glassy membrane was composed of collagenous rather than elastic tissue (Fig. 137). The immense thickening of the basement membranes that might occur in every follicle is demonstrated in Figure 138.

With the failure of formation of the internal root sheath, the hair shaft apparently took origin directly from the external root sheath by a process analogous to that of parakeratosis. The point of origin of the shaft came closer and closer to the surface as the matrix substance atrophied, and ultimately there remained only a bulbous plug of parakeratotic material near the mouth of the follicle (Fig. 139). This process was reflected in the structure of the cast-off hair (Fig. 140), which tapered near its formerly attached end and which was devoid of the remnants of the internal root sheath that usually adhere as a cuff.

The follicles, despite these changes, did not lose their capacity for regeneration, as shown in scalps from patients of group III (dying after the sixth week). The process of regeneration and the analogy with the normal processes of replacement of hair are described subsequently.

Other changes in the scalp were inconspicuous. There might be atrophy of the rete pegs and a general thinning of the epithelium at the surface, sometimes associated with hyperkeratosis (Fig. 138). The keratotic material was particularly abundant in the mouths of the hair follicles. Hyperpigmentation sometimes was observed in the scalps of these epilated patients. The pigment was situated in the basal layer of the epithelial cells. Atrophy of the sebaceous glands frequently was observed (Fig. 139). This process went hand in hand with atrophy of the hair follicle and cannot be interpreted as a direct radiation effect. The sweat glands in skin that had not been burned showed relatively little change, although occasionally the acini appeared shrunken and had thickened basement membranes and tiny vacuolated epithelial cells with pyknotic nuclei.

### *Group III: Patients Dying after the Sixth Week*

The patients of group III, those dying after the sixth week, as a rule showed the effects of malnutrition. By that time the bone marrow usually had recovered or had become hyperplastic, and there was evidence of the delivery of leukocytes to the lesions in the tissue. In occasional instances, however, there was evidence of a maturation

defect, and in a few patients the marrow remained hypoplastic. Concomitantly with the recovery of the marrow, hemorrhagic lesions were relatively rare despite the necrosis of some tissues.

The important lesions at the time of death were focal necrotizing pneumonia (sometimes in process of organization) and necrotizing enterocolitis. In both of these, polymorphonuclear leukocytes usually were now prominent elements of the exudate. It is probable that the depression of hemopoiesis that occurred for a time in many of these patients was the important factor in permitting these infections to gain headway. Stigmata of radiation effect, particularly epilation and testicular atrophy, were still present, but in some patients considerable regrowth of hair had occurred that was manifest in regenerative processes histologically.

Tables XXXII to XLVI include data for group III patients from Nagasaki, since in this group information regarding distance from the bomb was stated in the protocols.

The clinical data pertinent to the group III patients who were necropsied are given in Table XVI.

*Heart (Table XXXII).* Aside from hemorrhages and the apparently adventitious lesions regarded as "rheumatic," and for one instance each in which gross diagnoses of "fatty change" and "focal necrosis" were substantiated microscopically, there were no significant changes in the heart.

*Lungs (Table XXXIII).* Multiple pulmonary hemorrhages were noted in one instance. In most cases there were necrotizing lesions of the lungs heavily infiltrated with polymorphonuclear leukocytes. In two of these (Figs. 25 to 27) abscesses had formed, with fibrous walls surrounded by large zones of organizing pneumonia. In 3 patients there again was evidence of "neutropenic necrotizing pneumonia." The marrow of one of these, who had been heavily exposed to radiation, exhibited a very remarkable degree of hyperplasia and in the other cases the marrow was aplastic. Three patients died of advanced fibrocaseous pulmonary tuberculosis.

*Spleen (Table XXXIV).* In the spleen, the lymphoid tissue usually was still atrophic and atypical large mononuclear cells tended to persist, but there was evidence of recovery in some cases. In these there were now abundant lymphocytes about the central vessels of the malpighian corpuscles, and in many of them germinal centers had begun to appear (Fig. 48). In certain of the corpuscles of such patients a few groups of large reticulum cells were still discernible in compact arrangement at the periphery of the collars of mature lymphocytes.

TABLE XXXII

*Group III: Heart*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Gross specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Epicardial hemorrhages | 4 | | | | 2 | 1 | | |
| Endocardial hemorrhages | 1 | | | | | | | |
| Fatty change of myocardium | 1 | | | | | | | 1 |
| Focal necrosis of myocardium | | | | | | | | 1 |
| Additional observations | | | | | | | | |
| Fibrous pericardial adhesions | 1 | | | | 1 | | | |
| Chronic verrucous mitral endocarditis | 1 | | | 2 | | | | |
| Chronic verrucous tricuspid, mitral, and aortic endocarditis | | | | | | | 1 | |

TABLE XXXIII

*Group III: Lungs*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Histologic specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Focal atelectasis and emphysema | | | 1 | 1 | | | | |
| Multiple hemorrhages | | | | | | | 1 | |
| Focal neutropenic pneumonia | 2 | | 1 | | | | | |
| Focal necrotizing pneumonia with polymorphonuclear cells, all | 6 | | | | 4 | 2 | | 3 |
| Same (with organization) | 2 | | | | | | | 2 |
| Fibrocaseous pulmonary tuberculosis | | | | 2 | | | | 1 |
| Fibrinous pleurisy | 1 | | | | | | | |
| Additional diagnoses | | | | | | | | |
| Fibrous pleural adhesions | | | | 2 | 1 | | 1 | 1 |
| Healed tuberculous foci | 1 | | 1 | | | | | |
| Interstitial pulmonary fibrosis | | 1 | | | | | | |
| Tuberculosis of tracheobronchial lymph nodes | | | | | | 1 | | |
| Hydrothorax | | | | | | | | 1 |

TABLE XXXIV

*Group III: Spleen*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Histologic specimens available | 9 | 1 | 4 | 2 | 6 | 3 | 1 | 5 |
| Perisplenic adhesions | 2 | | | | | | | |
| Decrease of lymphocytes | 6 | | 3 | | 5 | 2 | | 2 |
| Many lymphocytes, no germinal centers | 1 | | 1 | 1 | | | | 1 |
| Absence of germinal centers | 7 | | 4 | 1 | 5 | 1 | | 2 |
| Germinal centers present | 2 | 1 | | 1 | 1 | 2 | 1 | 2 |
| Atypical mononuclear cells | 6 | | | | 3 | 1 | | 1 |
| Heavy plasma cell infiltration | 1 | | | | | | | |
| Focal necrosis (bacterial emboli) | | | 1 | | | | | |
| Infarct | | | | | | 1 | | |
| Hemorrhage in capsule | | | | | | | 1 | |
| Tuberculosis | | | | | | | | 1 |

*Lymph Nodes (Table XXXV).* The lymph nodes appeared to be even more laggard than the spleen in regard to restoration of germinal centers. They were present in the nodes of only one patient. Most lymph nodes still manifested loss of mature lymphocytes, compaction of reticulum and atypical large cells as previously described (Fig. 54).

TABLE XXXV
*Group III: Lymph Nodes*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Histologic specimens available | 6 | 0 | 1 | 1 | 5 | 1 | 1 | 1 |
| Decrease of lymphocytes | 5 | | 1 | | 5 | | 1 | 1 |
| Lymph nodes composed of typical lymphocytes, but without germinal centers | | | | 1 | | | | |
| Absence of germinal centers | 5 | | 1 | 1 | 4 | | 1 | 1 |
| Germinal centers present | 1 | | | | 1 | | | |
| Atypical mononuclear cells | 6 | | 1 | | 2 | | | |
| Additional diagnoses | | | | | | | | |
| Tuberculosis of tracheobronchial or hilar nodes | | | | | 1 | 1 | | |

*Bone Marrow (Table XXXVI).* Although the marrow might remain hypoplastic, there was usually at least focal regeneration (Figs. 69 and 70), especially in the myeloid series, and sometimes marked myeloid hyperplasia (Figs. 57 and 72). This was manifest in the long bones as well as in the ribs, sternum, and vertebrae. Most patients dying at this stage had a severe anemia that might in part be associated with the omnipresent severe infections.

In some of the marrows from Nagasaki patients, relatively large numbers of eosinophilic myelocytes existed.

A typical example of a group III marrow was found in K-50. In a section of vertebrae, the marrow appeared to be hyperplastic. The cells were supported within congested and even hemorrhagic tissue. The most numerous elements in the cellular population appeared to be the younger neutrophilic and eosinophilic myelocytes. There were relatively few late myelocytes, band cells, and mature polymorphonuclear leukocytes. Occasional blast forms were seen and some cells were in mitosis. There also were many megakaryocytes and numerous small islands of erythropoietic tissue. Fairly large numbers of plasma cells, some multinucleated, also were in evidence, together with lymphocytes and large stellate phagocytes filled with hemosiderin.

In sections of rib there was still an abundance of "gelatinous marrow," within which were islands of hemopoietic tissue, again containing a predominance of younger forms (Fig. 70). The tissue was essentially

similar to the vertebral marrow except for the relatively large amounts of acellular material.

The upper half of the shaft of a femur of this patient had a remarkable gross appearance (Fig. 34). The abundant marrow contained among the stout trabeculae of bone had a translucent currant-jelly appearance in

TABLE XXXVI

*Group III: Bone Marrow*

| Observations | Hiroshima | | | | Nagasaki* | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Long bones | | | | | | | | |
| Histologic specimens available | 6 | 1 | 3 | 3 | 1 | 1 | 1 | 1 |
| Type A: hypoplasia | 1 | | 2 | | | 1 | | |
| Type B: marked focal reticulum hyperplasia | | | | 2 | | | | 1 |
| Type C: focal myeloid regeneration | 4 | 1 | 1 | | 1 | | 1 | |
| Type D: marked myeloid hyperplasia | 1 | | | 1 | | | | |
| Flat bones | | | | | | | | |
| Histologic specimens available | 3 | 0 | 0 | 0 | 5 | 2 | 1 | 3 |
| Type A: hypoplasia | | | | | | | | |
| Type B: marked focal reticulum hyperplasia | 2 | | | | 1 | | | |
| Type C: focal myeloid regeneration | 1 | | | | 4 | 2 | 1 | 2 |
| Type D: marked myeloid hyperplasia | | | | | | | | 1 |
| No bone marrow | | | | | | | | |
| Polymorphonuclear cells in tissues | | | 1 | | | | | |
| Additional diagnosis | | | | | | | | |
| Caseous tuberculosis of marrow | | | | | | | | 1 |

* The case of monocytic leukemia is not tabulated with the others.

part, but this tissue contained foci of much more opaque gray-red or pale red-brown substance. This was yielded in large friable fragments to the knife. In smears of this tissue there were clumps of young cells with coarsely reticular nuclei and abundant basophilic cytoplasm. These often were associated with islands of normoblasts and were identified as basophilic erythroblasts. There also were myelocytes and scattered plasma cells within an abundant "gelatinous" matrix.

Smear preparations of these various tissues stained by the Wright-Giemsa method were excellently preserved (Fig. 71). The only unusual feature was the presence of relatively large numbers of lymphocytes and of plasma cells, some of which were multinucleated. The granules of the myelocytes were well stained everywhere, even in the youngest forms. There were some cells resembling myelocytes, but with clear cytoplasm. These might be forms intermediate between the reticular elements and the myelocytes. Band cells and a few polymorphonuclear leukocytes also were found.

The background substance in "gelatinous marrow," as seen in K-50, deserves comment. It had a delicately fibrillar structure, which was apparent in the hematoxylin and eosin preparation. In Masson and phosphotungstic acid hematoxylin stains, this material gave the reaction of fibrin (Fig. 74). It was deposited most densely about cells, some of which had the structure of megakaryocytes. Smaller elements, more like reticulum cells, and some cells intermediate between these and megakaryocytes also acted as centers upon which fibrin was deposited (Fig. 73).

Relation to Peripheral Leukocyte Count. Relatively few patients who lived beyond the sixth week exhibited a persistent leukopenia. In patients who did not develop a leukocytosis in response to an acute infection, the bone marrow at necropsy showed either evidence of maturation defect and was hyperplastic, as in the case which has just been described, or the marrow showed varying degrees of hypoplasia. In K-50, despite the hyperplasia of the marrow demonstrated in Figures 34 and 70, the peripheral white blood cell counts did not exceed 6500.

*Laboratory Data—K-50*

| | Date of examination of blood | | | |
|---|---|---|---|---|
| | Sept. 19 | Oct. 8 | Oct. 15 | Nov. 8 |
| Red blood cells (*millions*) | 2.2 | 1.5 | 1.8 | 1.7 |
| Hemoglobin (*per cent*) | 36 | 31 | 62 | 35 |
| White blood cells | 3200 | 5100 | 6500 | 4300 |
| Polymorphonuclear cells, mature (*per cent*) | | | 47.5 | 8 |
| Band cells (*per cent*) | | | 25 | 53 |
| Metamyelocytes (*per cent*) | | | 6 | 8 |
| Myelocytes (*per cent*) | | | 0 | 5 |
| Lymphocytes (*per cent*) | | | 13.5 | 14 |
| Monocytes (*per cent*) | | | 8 | 7 |
| Eosinophils (*per cent*) | | | 0 | 3 |
| Basophils (*per cent*) | | | 0 | 2 |

Reticulocytes (Oct. 15, 1945): 18 per cent
Platelets (Oct. 15, 1945): 45,900 per cmm.
Protein ($CuSO_4$ method): 6.6 gm. per cent

Notable features of the counts were the anemia, and the shift to the left in the granulocytic series. A large number of reticulocytes also was observed, indicating a regenerating but as yet insufficient erythropoietic tissue. This patient died on November 15, 1945, of a necrotizing and organizing pneumonia (Figs. 25 and 27).

In most patients surviving into the third period, there was leukocytosis associated with hyperplasia of the bone marrow, despite previous leukopenia. K-118 (sub-group 311) is an example.

*Clinical History—K-118*

K-118 was a 56-year-old woman who was at 700 yds. She was thrown a distance by the blast and sustained slight contusions of the back and the legs. At the time

of the bombing she was out of doors cutting grass close to a wooden Japanese building. Few observations were recorded in the clinical history. There was nausea but the date of its occurrence was not stated. On August 26 diarrhea appeared which persisted to the time of death. It was of sanguineous type. Epilation was present but the date of onset was not stated, and there was also pigmentation of the skin. The patient was unconscious shortly after the blast and was carried to the village of Izumite where she regained consciousness. During the entire course she had only a slight fever. She died on October 5, 1945.

| | *Red blood cells* | *White blood cells* |
|---|---|---|
| August 29 | 2.44 millions | 1050 |
| September 1 | 1.74 millions | 570 |
| September 7 | 3.30 millions | 1040 |
| September 15 | 5.31 millions | 2900 |
| September 25 | 3.92 millions | 3600 |
| September 29 | 3.72 millions | 11,400 |
| October 1 | 3.85 millions | 17,700 |

The important lesions at necropsy were hemorrhagic pneumonia and ulcerative ileocolitis.

The bone marrow showed reticulum hyperplasia (type B), as illustrated in Figure 69, and there was considerable differentiation into myeloid tissue, but numerous plasma cells were still present. In the lymph nodes of this patient there was lymphoblastic hyperplasia but there was no evidence of leukemic infiltration of the tissues.

In some instances, myeloid hyperplasia in patients dying in this period was extreme and the adipose tissue of the marrow had almost completely disappeared (K-14, Fig. 72). The marrow in this case was of type D. This patient had a moderate leukocytosis before his death from acute suppurative renal disease on September 22, 1945.

A single instance of leukemia was encountered during the study of some 14,000 patients in both cities. Although this case is considered purely adventitious, it is presented in detail for the reason that the patient had been close to the bomb and had had a striking leukopenia before the leukemia developed.

### *Case Report*; M. Matsuo, Autopsy K-224*

The patient was a 19-year-old schoolboy, who was at a munitions factory in Nagasaki, approximately 1000 yds. removed from the center. He lost consciousness and sustained a slight burn of the right leg at the bombing. A few days later he suffered from anorexia but gradually recovered. On August 28, epilation appeared and on September 3 there was fever accompanying the onset of petechiae and sore throat.

He was admitted to the hospital on September 8, when there were petechiae over the whole body, particularly upon the abdomen. The pharynx was congested but

* Abstracted, in part, from "Report of a Case of Monocytic Leukemia Occurring Following the 'Atomic Bomb Disease'" by Dr. Tando Misao, Dr. Yoshimichi Harada, and Dr. K. Hattori, Faculty of Medicine, Kyushu Imperial University.

there was no necrosis. At that time there was a marked decrease in the red blood cell count although the hemoglobin was recorded as "100 per cent." There was marked leukopenia and the sedimentation rate was increased. The nucleated cells of the marrow were found to be 22,600 per cmm. and there was an excess of lymphocytes and plasma cells. Vitamin B and liver extract were administered and the bones were irradiated with ultraviolet light. The patient improved, the white blood cell count reaching 5500 shortly before his discharge on September 30, 1945. His red blood cell count was then 3.29 millions with 77 per cent hemoglobin.

He returned to school after leaving the hospital and had no complaints. For 3 days after November 4 he worked hard at the rice harvest, but complained of a tired feeling. On the evening of November 6 there was a sensation of fever accompanied by headache, swelling of the gums with bleeding, pharyngitis with pain in the throat and difficulty in swallowing. The next day he had a high fever and there were petechiae of the extremities. On November 9 he had some sanguineous stools and was readmitted to the hospital on November 12. At that time his pulse rate was elevated to 120. There was edema and pallor of the face. Petechiae were seen everywhere in the skin and on the buccal mucous membrane. The gums were swollen. The soft palate, particularly on the right side, was remarkably swollen and was partly covered with a thick white membrane. There was gangrene of the right tonsil. Erosions were observed on the nasal mucous membrane and there was hemorrhage from the drum of the left ear. Hemorrhages were seen also on each retina. The cervical lymph nodes were enlarged to the size of a thumb and several axillary nodes of this size were palpated also. Both the liver and spleen were found to be slightly below the costal margin upon clinical examination.

Laboratory examinations showed a few red blood cells in the urine. The stools were tarry and diarrheal, and were strongly positive for blood. Hematologic examination showed a white blood cell count of 390,000 with a predominance of cells thought to be monocytes (Fig. 75). Eighty-one per cent of these cells phagocytized carbon in living preparations (Fig. 76). Two and one-half per cent of all cells were positive by the peroxidase reaction and 0.9 per cent of the monocytes were positive. The nucleated cells of the marrow numbered 566,400 per cmm., of which 91.2 per cent consisted of monocytes, including many young forms. A few of these cells were in mitosis and some vacuolated forms were found also. The hepatic and splenic punctures showed cells of similar type.

Course in Hospital. His temperature was sustained at 39° to 40° C. and the pulse rate was 100 to 120. He was given 1000 cc. of Ringer's solution, vitamins B and C, "cardiac tonics," and gargles. At approximately 1:30 a.m. on November 16, dyspnea appeared, the respiratory rate being 44 to 48, there was tachycardia of 140 to 160, and he died a few hours later in collapse.

The important laboratory and temperature data are summarized in Text-Figure 2.

### *Findings at Necropsy: Gross Notes*

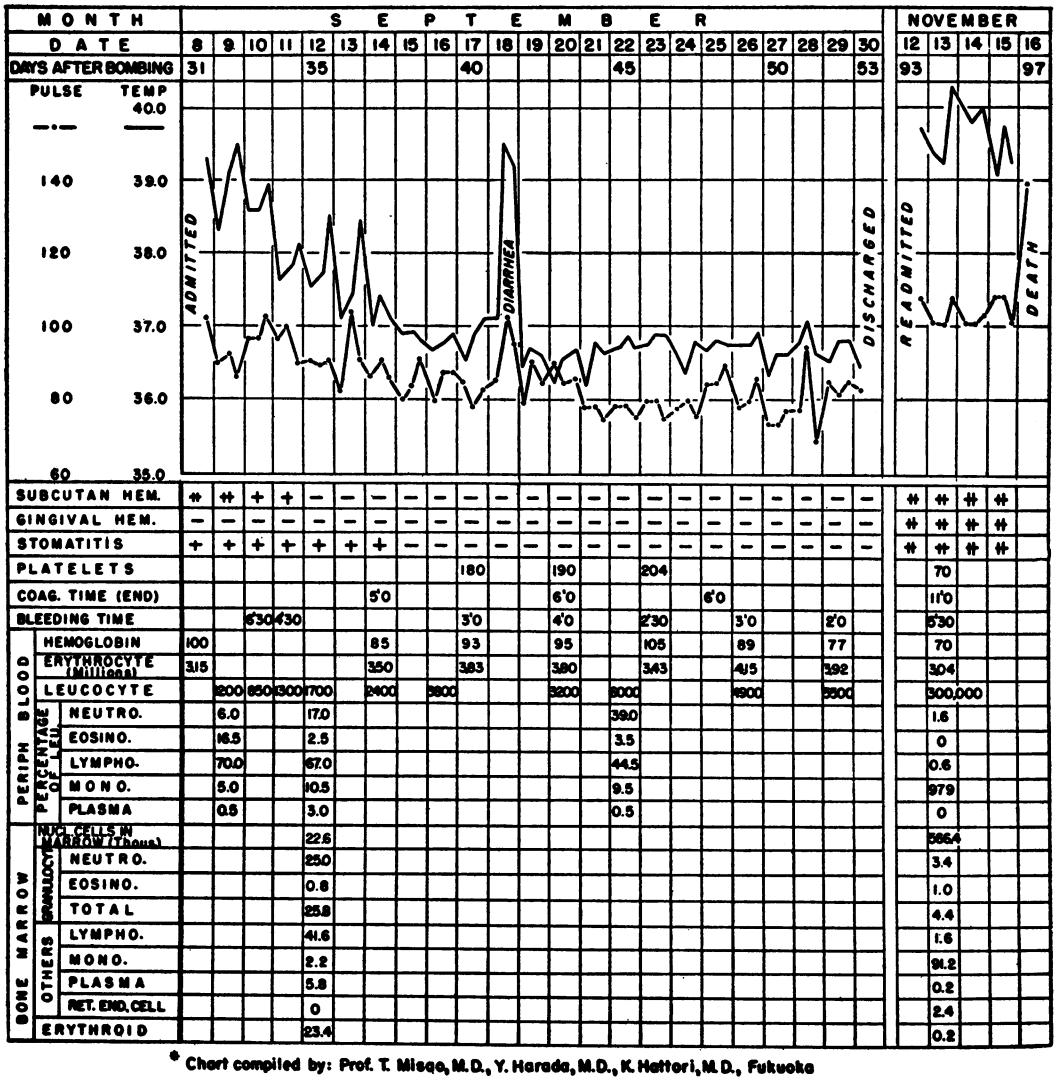
There were petechiae of the skin, pericardium, pleura, peritoneum, Glisson's capsule, renal pelves, pharynx, esophagus, large intestine, and submucosa of the oral cavity. Approximately 100 cc. of fluid blood were found in the peritoneal cavity. Small foci of hemorrhage were seen in the pulmonary parenchyma. There was necrosis of the right tonsil and a gray membrane involved both tonsillar regions and the soft palate. On the mitral valve a few verrucous masses were seen. Focal pneumonia was found in the right lower lobe. The spleen weighed 230 gm. and on the cut surface had an irregularly mottled, dark red appearance. The trabeculae were indistinct. The lymph nodes of the cervical, mediastinal, and axillary regions were enlarged as were those of the stomach and intestines. Hemorrhagic erosions and small ulcers were seen throughout the gastro-intestinal tract. Pyramidal yellow-gray zones were found in the kidneys which were thought to be infarcts.

*Histologic Notes*

Large numbers of mononuclear cells were found throughout most of the tissues. The cells occurred in closely compacted groups and consequently some were polygonal in outline, and an occasional cell was spindle shaped. Most of the cells presented spherical or slightly indented nuclei with prominent nucleoli. The cytoplasm apparently was much less abundant than in the cells seen in the peripheral blood. In many places groups of the atypical cells had become necrotic.

Such mononuclear infiltrations were situated among the muscle fibers of the heart,

**MONOCYTIC LEUKEMIA***




* Chart compiled by: Prof. T. Misao, M.D., Y. Harada, M.D., K. Hattori, M.D., Fukuoka

Text-Figure 2

some of which consequently became atrophic. The small blood vessels of the interstitium also were filled with atypical cells.

The walls of the alveoli of the lungs were thickened by large numbers of the atypical mononuclear cells. There also was focal necrosis about the bronchioles, whose walls had become necrotic. Polymorphonuclear cells were not seen.

In the liver the pericentral sinusoids were especially involved and there were only occasional mononuclear cells in the periportal connective tissue (Fig. 79). The hepatic cell cords at their central ends had become strikingly atrophic.

In the intestines there were tremendous submucosal infiltrations but these were fewer in the mucosa. The latter, however, had become necrotic in many large foci.

In striated muscle (Fig. 78) there was massive infiltration of cells among the fibers, some of which had become atrophic. Occasionally one of the mononuclear elements was found in mitosis. Groups of cells had suffered necrosis, but for the most part the tissue was well preserved.

In the pharynx there were striking subepithelial infiltrations. The epithelium in the section available, however, appeared intact.

Large interstitial and perivascular infiltrations were found throughout the kidneys. Many cells of the mononuclear type also occupied a subcapsular position.

The lymph nodes consisted of solid masses of the mononuclear cells such as have been described previously. There were large foci of necrosis.

The small fragment of marrow (Fig. 77) that was available contained only a few large fat cells, but there were large septa composed of masses of mononuclear cells. These had the same structure as they had elsewhere in the tissues. No islands of erythropoietic or myelopoietic tissue of the usual type were seen.

The vessels of the brain contained large mononuclear cells in massive collections; there was no interstitial infiltration in this organ.

*Gastro-intestinal Tract (Table XXXVII).* Ulcerative lesions of the intestine, especially of the colon, occurred often in group III. They again tended to be superficial and to be covered with fibrin. Sometimes the foci

TABLE XXXVII

*Group III: Gastro-intestinal Tract*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| **Stomach** | | | | | | | | |
| Gross specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Acute ulcer | 1 | | | | | | | 1 |
| Petechiae | 4 | | 1 | 1 | | 1 | 1 | 2 |
| Plasma cell infiltration | | | | | | 1 | | |
| **Small intestine** | | | | | | | | |
| Gross specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Ulcerative enteritis | 1 | | 1 | | 2 | | | 1 |
| Petechiae | 1 | | | | | | 1 | 2 |
| Intussusception of ileum | | | | 1 | | | | |
| **Large intestine** | | | | | | | | |
| Gross specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Petechiae | 4 | | 1 | | | 1 | 1 | 2 |
| Ulcerative colitis | 2 | 1 | 3 | 2 | 2 | 2 | | |
| **Additional diagnoses** | | | | | | | | |
| Ascariasis | 2 | | | | 3 | | 1 | |
| Amebic colitis | 1 | | | | 1 | | | |
| Strongyloidosis | | | | | 1 | | | |

of necrosis bulged into the lumen despite destruction of the epithelium. Polymorphonuclear leukocytes might appear in the lesions. In at least one case, however, they contained relatively few of these cells despite the hyperplastic marrow, and the ulcers were histologically similar to those of the aplastic stage.

TABLE XXXVIII

*Group III: Liver and Gallbladder*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Microscopic specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Giant nuclei in pericentral hepatic cells | 1 | | | 1 | | | | |
| Central congestion, all | 3 | 1 | 1 | 1 | 2 | | 1 | 1 |
| Central congestion, with necrosis | 1 | | | | 1 | | 1 | |
| Edema of pericentral connective tissue | 2 | 1 | | | | | | |
| Focal fatty change of liver: | | | | | | | | |
| Periportal | 1 | | 3 | 1 | | 2 | | 2 |
| Midzonal | 3 | | | | | | | 1 |
| Pericentral | 2 | | | | | | | 1 |
| Disseminated | | | | | 1 | | | |
| Focal necrosis of liver | | | | | 2 | | | |
| Additional diagnoses | | | | | | | | |
| Calculi in gallbladder | | | 1 | | | | | |
| Chronic cholecystitis | | | | | | 1 | | |
| Ascaris in bile duct | | | 1 | | | | | |
| Calculus in choledochal duct | | | 1 | | | | | |
| Chronic cholangiitis | | | 1 | | | | | |
| Tuberculosis of liver | | | | | | | | 1 |

An intussusception of the ileum and localized peritonitis occurred in one patient. One case of amebic colitis was found in each series in this group (Fig. 92).

*Liver (Table XXXVIII).* Fatty changes in the liver were much more common at this stage than in the preceding groups of patients. They probably were associated with malnutrition and other factors rather than radiation. The change usually was mid-zonal or periportal and sometimes involved as much or more than one-half of the lobule. Necrosis, apparently in association with central congestion, was in evidence in 3 instances (Fig. 95). The mechanism of the central congestion was not clear as there were no evidences of acute lesions of the myocardium in these patients, despite the verrucous endocarditis that was occasionally encountered, nor were there chronic lesions such as a significant degree of mitral stenosis to account for the congestion. However, complete and detailed gross descriptions of the heart and detailed clinical information were not available. Disseminated foci of necrosis were encountered in 2 instances.

*Pancreas.* No significant lesions were discovered in the pancreas. The acini frequently were small, perhaps in association with the mal-

nutrition, but otherwise the cells were typical in structure and there was no evidence of fibrosis.

*Kidneys (Table XXXIX).* The kidneys exhibited no specific lesions. In one case there were multiple abscesses and another showed pyelonephritis. Polymorphonuclear leukocytes were present in large numbers

TABLE XXXIX
*Group III: Kidney*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Histologic specimens available | 8 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Hemorrhage of pelvis | 2 | 1 | 1 | | 1 | | | |
| Cloudy swelling | 3 | 1 | 1 | | 1 | | | 2 |
| Scars of kidney | 3 | 1 | 1 | | 1 | 1 | | 1 |
| Abscesses (with polymorphonuclear cells) | 1 | | | | | | | |
| Atypical small and large mononuclear cells in sinusoids | 1 | | | | | | | |
| Infarcts | | | | | 1 | | | |
| Acute pyelonephritis | | | | | | 1 | | |
| Additional diagnoses | | | | | | | | |
| Leiomyoma of renal pyramid | 1 | | | | | | | |
| Calculus of pelvis | | | | | 1 | | | 1 |
| Tuberculosis | | | | | | | | 1 |

in these lesions. In one patient there were the large and small mononuclear cells within the corticomedullary sinusoids that have been described previously.

*Ureters and Bladder.* There were petechiae of the bladder in 2 cases of sub-group 311 and in one of sub-group 312.

*Testes (Table XL).* In this group, all members of which were malnourished, the testicular atrophy was much more complete than in the preceding group (Figs. 39 and 105). The basement membranes usually were thickened and the Sertoli cells might be shrunken. Within the old

TABLE XL
*Group III: Testes*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Histologic specimens available* | 5 | 1 | 3† | 2 | 2 | 2 | 0 | 2 |
| Atrophy of germinal epithelium and derivatives | 5 | 1 | 1 | 2 | 2 | 2 | | 2 |
| Thickening of basement membranes of tubules | 5 | 1 | 1 | 1 | 2 | 2 | | 2 |
| Hyaline changes of blood vessels | 4 | | | 1 | | | | |
| Hyperplasia of interstitial tissue | 3 | | | 1 | | 1 | | |
| Infantile testis | | | 1 | | | | | |
| Atrophy of Leydig cells, with hyperpigmentation | | | | | | 1 | | |

* All are from malnourished patients.
† One patient, 83 years of age, showed active spermatogenesis.

basement membranes there appeared in a broad band a less cellular, delicately fibrillar connective tissue. Spermatogenic tissue had completely disappeared. The tubules had shrunken and occasionally were completely hyalinized. The small blood vessels often had brightly acidophilic deposits of material beneath the endothelium and muscular wall, as seen in the earlier stages. In many cases there was now, in the opinion of one of us (A. A. L.), definite hyperplasia of interstitial tissue.

*Prostate.* An 83-year-old man, K-66, who was reputedly at 1800 yds., had an adenocarcinoma of the prostate. The testes of this patient, despite his age, were among the very few that showed no evidence of atrophy. In K-50, an emaciated 31-year-old man dying on the 100th day, in whom the testes were extremely atrophic, the prostate also was remarkably small grossly, as were the acini and epithelial cells histologically (Fig. 107).

*Ovaries (Table XLI).* In 5 premenstrual females who were within 1500 yds., numerous primordial follicles were still present. Developing

TABLE XLI

*Group III: Ovaries, Uterus, Fallopian Tubes, and Vagina*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Ovaries | | | | | | | | |
| Histologic specimens available | 4 | 0 | 1 | 1 | 3 | 0 | 1 | 3 |
| Postmenopausal | 1 | | 1 | | | | 1 | 1 |
| Premenarche | 1 | | | 1 | 2 | | | 1 |
| Developing follicles absent,* corpora albicantia present | 2 | | | | 1 | | | 1 |
| Hemorrhages | | | | | | | 1 | |
| Uterus, fallopian tubes, and vagina | | | | | | | | |
| Histologic specimens available | 1 | 0 | 1† | 0 | 1 | 1 | 0 | 1 |
| Endometrium in resting phase | 1 | | | | 1 | | | |
| Myomata | | | 1 | | | | | |
| Endometriosis | | | | | | 1 | | |
| Acute salpingitis | | | | | | 1 | | |
| Tuberculosis | | | | | | | | 1 |
| Chronic vaginitis | | | | | | | | 1 |

* In premenopausal mature women.

† Postmenopausal.

follicles were absent in 3 in whom both corpora albicantia and primordial follicles were in evidence. Atrophy was much less evident than in the male.

*Brain (Table XLII).* Suppurative complications in the brain were relatively frequent. In this group there were 2 patients with suppurative meningitis and one with a "cerebral abscess." The abscess might possibly have been a tuberculous lesion since the patient had caseating pulmonary tuberculosis, but histologic sections were not available.

TABLE XLII
*Group III: Brain*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Gross specimens available | 8 | 1 | 4 | 3 | 6 | 2 | 1 | 6 |
| Histologic specimens available | 5 | 0 | 3 | 1 | 1 | 0 | 0 | 0 |
| Petechiae of cerebrum | 1 | | 1 | | | | | |
| Suppurative meningitis with polymorphonuclear cells | 2 | | | | | | | |
| Abscess of occipital lobe* | | | | 1 | | | | |
| Thrombus in superior longitudinal sinus | 1 | | | | | | | |
| Additional diagnoses | | | | | | | | |
| Senile plaques | | | 1 | | | | | |
| Microgyria | | | 1 | | | | | |
| Cystic change of lenticular nucleus | | | 1 | | | | | |

* Gross specimen only.

*Adrenals (Table XLIII).* The atrophy that has been noted previously in the adrenal glands was extreme and in some cases involved all layers (Fig. 115). Usually the outer portion of the zona glomerulosa showed the most striking changes. Again it must be emphasized that most of these patients were emaciated.

TABLE XLIII
*Group III: Adrenals*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Gross specimens available | 9 | 1 | 4 | 3 | 5 | 3 | 1 | 5 |
| Histologic specimens available | 8 | 1 | 3 | 3 | 5 | 3 | 1 | 5 |
| Gross evidence of loss of lipid, no microscopic sections available | | | 1 | | | | | |
| Atrophy of cortex, especially of the zona glomerulosa | 6 | 1 | | 1 | 5 | 2 | 1 | 5 |
| Focal fatty changes of cortical epithelium | | | 1 | | 1 | 1 | | |
| Focal necrosis of cortical epithelium | | | 1 | | | 1 | | |
| Periadrenal hemorrhages | | 1 | | | | | 1 | |
| Hemorrhages of cortex | 1 | | 1 | | | | 1 | |
| Chronic passive congestion | 2 | | | | | | | |
| Additional diagnosis | | | | | | | | |
| Tuberculosis | | | | | | 1 | | 1 |

*Thyroid Gland (Table XLIV).* Occcasionally in these emaciated patients the thyroid showed variation in the size of the follicles. In such thyroids there were many minute follicles lined by low-cuboidal epithelium, and thick septa of connective tissue infiltrated with lymphocytes traversed the organ. The significance of this lesion is difficult to assess. Four of 6 patients showing this change were stated to have been beyond 1500 yds.

*Pituitary Body.* Six pituitary glands were available in histologic sections. In K-50 the basophilic cells were remarkable for their large

size. A few were vacuolated. They were present in groups in all parts of the gland. The eosinophilic cells, on the contrary, were minute and inconspicuous. The changes in the pituitary body were much less striking than in K-42, Figure 37. The testis of K-50 is illustrated in Figure 105.

TABLE XLIV

*Group III: Thyroid Gland*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Gross specimens available | 8 | 1 | 4 | 2 | 5 | 3 | 1 | 6 |
| Histologic specimens available | 4 | 0 | 0 | 1 | 4 | 2 | 1 | 5 |
| Slight increase of interstitial tissue, and lymphocytic infiltration | 1 | | | 2 | 1 | | | 2 |

TABLE XLV

*Group III: Mouth and Neck Organs*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Histologic specimens available | 7 | 1 | 4 | 2 | 6 | 3 | 1 | 6 |
| Gingivitis, all types | 3 | | | | 1 | | | 1 |
| Hemorrhagic | 2 | | | | | | | |
| Necrotizing | 1 | | | | 1 | | | |
| Necrotizing focal tonsillitis | 4 | 1 | 2 | 1 | | | | |
| Scars of tonsils | 1 | | | | | | | |
| Chronic glossitis | | | | | | | | 1 |
| Laryngitis | | | | | 1 | | | |

One other pituitary body showed slight vacuolation of the basophils, whose number, however, was small. The patient was a 78-year-old woman. This change was found constantly in senile females.[77]

*Mouth and Neck Organs (Table XLV).* Necrosis of the tonsils sometimes occurred in this group, but it usually was focal rather than diffuse. In one case microscopic sections showed evidence of necrosis without leukocytic infiltration, but there was hypoplasia of the bone marrow. In others, in which the marrow was not aplastic, polymorphonuclear cells were found within the necrotic tissue lining the crypts. There was no hemorrhage. Necrotizing gingivitis occasionally was still in evidence. There usually was no necrosis of the larynx or epiglottis.

*Skin (Table XLVI).* Petechiae in the late cases were unusual. Hair follicles often showed evidence of regeneration. There were renewed differentiation of the internal root sheath, regrowth of the papilla, decrease in the thickness of the basement membrane, and a new hair shaft was found on its way outwards through the plug of keratinized epithelium at the mouth of the follicle. A completely atrophic follicle showing all of these changes described in group II is illustrated in Figure 141. In

TABLE XLVI
*Group III: Skin*

| Observations | Hiroshima | | | | Nagasaki | | | |
|---|---|---|---|---|---|---|---|---|
| | Sub-group | | | | Sub-group | | | |
| | 311 | 312 | 321 | 322 | 311 | 312 | 321 | 322 |
| Gross specimens available | 9 | 1 | 4 | 3 | 6 | 3 | 1 | 6 |
| Epilation | 5 | | 1 | 1 | 2 | 1 | | 3 |
| Hemorrhages | | | | | 3 | 2 | | 1 |
| Decubital ulcers | | 1 | | 1 | 3 | 2 | | 2 |
| Eczema | | | 1 | | | | | |

Figure 142 are shown the beginnings of the regenerative process. This process of atrophy and regeneration was a recapitulation of the usual processes of loss and replacement of the hair. It has been described in detail by Auburtin[6] (Fig. 143). In the adult, hair usually grows from the same root for 3 or 4 years. Then there is failure of differentiation of the internal root sheath, the basement membrane thickens, pigment becomes irregularly distributed, and the hair is extruded, just as in the irradiated persons. Regeneration takes place apparently from the same follicle and the keratinized tip of the new hair, capped with a new internal root sheath, burrows its way through the old plug at the mouth of the follicle. In the irradiated person the process was condensed in time and involved the great majority of follicles. Perhaps also in these follicles the atrophy was more complete, the thickening of the glassy membrane was greater, but regeneration nevertheless occurred. Regeneration was evident clinically in individuals with severe epilation within 7 weeks after the explosion.

In emaciated individuals of this group decubital ulcers occasionally occurred, as was to be expected.

## DISCUSSION

### *Mechanism of Death*

The factors responsible for death from radiation effect are not entirely clear, especially in those patients dying within the first 2 weeks. It is possible experimentally with x-rays to produce deaths "under the beam" if the dose is delivered at a sufficiently rapid rate.[39,69,83] Henshaw[39] has demonstrated histologically the widespread damage to tissue that may occur within 3 hours in animals receiving 25,000 to 50,000 r. at a rate of 250 r. per minute. Whether any of the population at Hiroshima and Nagasaki undamaged by burns or trauma died of such direct destruction of tissue within the first few hours is not known, since the first autopsies were not performed until 3 days after the bombing. During these first few days no clinical records of blood pressure were made, nor of fluid

balance studies. Thus the contribution of "shock" to radiation sickness cannot be evaluated.[60]

There is evidence of widespread damage to tissue of the same histologic pattern as that seen in animals succumbing within the first day after overwhelming doses of radiation. In the absence of bacteriologic studies, however, it is not possible to state with certainty that bacteria did not contribute to the early mortality, for even minor injuries and burns did not often escape infection. At 11 days the intestine of a patient at Nagasaki already showed large masses of bacteria lying within necrotic and edematous tissue in the mucosa (Fig. 83).

Few experimental studies have been concerned with the study of the generalization of infection after irradiation. Warren and Whipple[93] did not find evidence of an overwhelming bacterial invasion from the intestines of dogs dying within the first 4 days. Chrom,[16] using heavy doses of x-rays, found bacteria localized to the mesenteric lymph nodes within the first few days and generalization only after the seventh day. Similarly, after neutron or x-ray irradiation of animals, Lawrence and Tennant[49] found the blood and tissue cultures to be sterile within the first 4 days of radiation, but that "as the doses are decreased and the animals live longer, bacteremia is a usual finding and infection probably a more important factor in the cause of death."

After the second week heavily infected necrotic and ulcerated lesions in the skin, mucous membranes, and respiratory tract were invariably observed, and there was also in some instances, although cultures were not made, morphologic evidence of generalization of the infection with masses of bacteria in freshly fixed organs as remote from the surface as the brain (Fig. 114), bone marrow (Figs. 66 to 68), and eye.[95] Thus, in those patients who survived longer, infection appears to have become an increasingly important factor. Even localized infections can, under certain circumstances, contribute to the depression of bone marrow with resultant leukopenia and anemia.[19] Many of the lesions are indistinguishable from those seen in patients with aplastic anemia of other causation where, again, bacterial infection likewise is of primary importance in the mechanism of death. Infection, once established, can also affect the regenerative process in the tissues.

The definitive answer concerning the rôle of bacteria in increasing mortality and preventing recovery following irradiation will not be forthcoming until aseptically reared animals are exposed.

The interpretation of the histologic changes observed in these patients is rendered difficult not only by the factor of infection, but by the possible

influence of one damaged organ upon another. As far as hemopoiesis is concerned, Lawrence, Valentine, and Dowdy,[50] in cross-circulation experiments, found no evidence of an immediately operative humoral effect. Experiments of this type, however, do not completely solve the problem. An example is the appearance of "castration cells" in the pituitary body after destruction of the spermatogenic tissue of the testis. The careful analysis necessary before ascribing any changes to the direct action of ionizing radiations is well illustrated by the series of studies of the adrenal of the rabbit carried out by Engelstad and Torgersen.[23,25,81] In the last of a series of papers, Torgersen[81] concluded that the changes originally ascribed to the irradiation of the adrenal were in fact brought about indirectly. The histologic changes themselves that are observed after radiation are not specific, and every change can individually be produced by some other means.

### *Mitosis and Cell Activity*

Some of the effects of ionizing radiation on mitosis and activity of cells are now well known. The first autopsies came too late to detect whatever effect there may have been upon suppression of mitosis, which is stated by some to be a sensitive indicator of the action of ionizing radiations.[87] During the first few days many of the mitotic figures in the intestine, spleen, and elsewhere were atypical, and numerous bizarre cells, some with giant nuclei, appeared in these tissues. In the hemopoietic tissues the cells were so atypical as to resemble those found in Hodgkin's disease. "Micronuclei" appeared as in cells under the influence of colchicine.[14,80] Similar effects on mitosis and the presence of atypical cells have frequently been noted in the heavily radiated tissues of animals and men.[26,57] It is probable that most of these cells are not long viable, since after the second week they became increasingly rare in the tissues of the atomic bomb patients. Maximow[57] came to the same tentative conclusions in his studies of irradiated connective tissue, although he did not consider them definitive. The proliferative capacity of many tissues, however, if at all damaged, was soon restored, as demonstrated by the reticulum cells in the hemopoietic tissues, and the Sertoli cells in the testes. Phagocytic activity likewise was in evidence in the ingestion of red blood cells by the reticulo-endothelial cells of the bone marrow and spleen. Subsequently hemosiderosis developed, as described in the early observations of Heineke.[34] Again the factor of infection must be taken into account in considering the pathogenesis of this process.

### *The Blood-Forming Organs*

The sequence of changes in the peripheral blood in the population exposed to the atomic bomb was, in general, similar to that known to occur in animals and men exposed to adequate rapidly administered doses of ionizing radiations, as contrasted with repeated minute doses.[44,53] The first counts were made too late, however, to observe the initial leukocytosis so commonly found in the first few hours[21,37,38,59] in irradiated animals and patients. The initial polymorphonuclear (and with relatively small doses, lymphocytic[37]) leukocytosis probably represents a "mobilization rather than new formation"[11] of cells.

The first counts in the patients, made at Nagasaki on the first day after the bombing and at Hiroshima on the fourth, already indicated a leukopenia which became increasingly severe during the succeeding weeks.[47] The platelet counts fell later than the leukocyte counts and the erythrocyte levels sank more gradually than either.[21,69] Despite the very severe aplastic anemia, young forms of the white and red blood cells sometimes appeared in the peripheral blood during the first 10 days.

The disappearance of mature lymphoid cells from the lymph nodes, spleen, and thymus was striking even in the first available sections of the fourth day. Experimentally, during the administration of massive doses of x-rays, Henshaw[39] found striking destruction within the first 3 hours after the radiation was started. In the atomic bomb patients the cells seemed to undergo autolysis *in situ* and there was little evidence of their phagocytosis as described by Tsuzuki,[83] Henshaw,[37] and others. The slow restoration of the lymphocyte count was associated in these patients as well as in experimental animals with the slow recovery of the lymphoid tissues observed histologically.[11,21]

Similar rapidly destructive changes in the bone marrow were produced by Henshaw[39] within 3 hours during massive irradiation. In the patients, tissue from a cancellous bone was not available until the tenth day, but at that time there was almost total loss of the usual hematopoietic substance. In the subsequent 3 weeks, some marrows showed persistence of erythroblastic foci despite disappearance of granulopoietic tissue. This finding in irradiated bone marrows has been reported by Dunlap.[21] Bloom's[10] statement that the erythroblasts are exceedingly sensitive was not confirmed in the present material.

Remarkable was the resistance to destruction of the reticulum cells. A skeleton of these elements remained in the lymph nodes, skin, and bone marrow despite complete destruction of all mature cells. This

radio-resistance of the "macrophage system" has been noted by Bloom.[10] The reticulum cells retained their morphologic integrity even after the devastating doses employed by Henshaw.[39] Remarkable also was the regenerative capacity of reticulum cells. Proliferation of these elements was already in evidence by the sixth day in the earliest available specimen of a long bone. Different patients varied in the extent of regeneration, but when it occurred, the long as well as the flat bones took part in the regenerative process. The large agranular pale cells might form focally or diffusely distributed masses of stellate or rounded elements. They were described very early by Heineke[36] in regenerating marrows following external radiation, and by Martland[55] in marrows of patients who had ingested radium or mesothorium. Martland considered this "regenerative leukopenic anemia" the result of internal, as contrasted with external, radiation which in his view resulted in an aplasia of the marrow. This is certainly belied by the appearance of the marrows of many patients dying some 6 weeks after the atomic radiation. Hyperplastic bone marrows likewise may occur in individuals with "aplastic anemia" not produced by ionizing radiation, as described by Rhoads and Miller,[71] who also described large pale cells similar to those of the early phase of regeneration after the atomic bomb radiation. In the heavily irradiated patients these cells appeared at first to differentiate by a gradual series of transformations into plasma cells. After the first month, however, such cells appeared in some patients to acquire azurophilic granules and to be connected by a series of transition forms with myelocytes. Often deeply basophilic blast cells were present in such marrows, but in relatively small numbers, suggesting that the reticulum cells can be transformed quickly into myelocytes. Later, hyperplastic marrows of more usual structure, but retaining for some months unusually large numbers of plasma cells and lymphocytes, might be seen. This sequence of events was actually traced by repeated bone marrow aspiration studies in a series of patients[47] and is not described merely from the histologic appearance of bone marrows of patients dying at various times after the irradiation.

As Dunlap[21] and Rhoads and Miller[71] have pointed out, the cellularity of a bone marrow is not necessarily an index of the rate of delivery of cells to the peripheral blood. The nature of the "maturation defect" in some of the hyperplastic marrows is completely unknown. Perhaps the "defect" lies in the supply of some essential substance, as in pernicious anemia, or possibly the infections that accompany the phase of severe depression of the marrow are responsible. Certainly a major

therapeutic effort should be made to eliminate the factor of infection pending the resumption of more orderly hemopoiesis.

The mechanism of hemorrhage after irradiation recently has been illuminated by the studies of Allen and Jacobson[4] who demonstrated the appearance in the blood of a substance with the properties of heparin. This work, unfortunately, was unknown to the physicians in the field at Hiroshima and Nagasaki. It must be stated, however, that these observers were puzzled by the appearance of hemorrhages in patients whose levels of platelets had not fallen to values when hemorrhages usually occur.[47] The source of the heparin is unknown although mast cells were found early in relatively large numbers in the bone marrows and lymph nodes of the irradiated patients and later in the submucosa of the intestines beneath ulcerative lesions. The presence of mast cells in large numbers in the tissues is not necessarily indicative of hyperheparinemia, as Oliver[66] has shown in his observations of dogs with mast cell tumors. Toward the end of the first month, however, platelets in patients with a severe radiation effect often fell below 10,000 per cmm., a level at which cutaneous hemorrhages could be expected. The importance of thrombopenia as such in the mechanism of hemorrhage has likewise been recognized by Allen and his co-workers.[3]

Eosinophilia occasionally has been found in animals and patients after irradiation and was observed in some of the Nagasaki patients. The mechanism of the eosinophilia is obscure. There is some question, however, as to whether there may not have been exposure to renewed hookworm or other infections by parasites in these patients, who were thrust into unhygienic surroundings after their displacement from the city. It is interesting to note that Jacobson and Marks[44] found no evidence of eosinophilia in animals irradiated daily for long periods with 0.11 to 8.8 r. of gamma rays.

### *The Gonads*

It was realized from the first by Albers-Schönberg,[1] the discoverer of the sterilizing effects of x-rays, but often lost sight of by his successors, that mere histologic changes in the testes must be distinguished from the condition of sterility by the test of mating after an adequate interval of time. As Warren[88] has stated, the testis is not far different histologically whether in temporary or in permanent azoospermia; in the former condition a lesser number of germinal epithelial cells appears to have been destroyed. In the patients exposed to the atomic bomb, the testes showed profound destructive changes beginning as early as the

fourth day when the first material was available for histologic examination. The changes became more profound in succeeding weeks, but additional factors—infection and starvation—probably became concerned in the pathogenesis. In many of these patients a few spermatogonia still remained in close association with the basement membrane. A controlled clinical study was performed some 10 weeks after the explosion by examining active and well nourished men who had been relatively close to the center. In many of these, sperm counts revealed hypospermia and azoospermia in contrast with the findings in a group of prisoners who had been just beyond the range of radiation. Follow-up studies on the exposed men will be necessary, however, to establish whether permanent or temporary azoospermia has been produced.

The relation of the testicular atrophy to the appearance of "castration cells" in the pituitary body is of interest. Similar changes in the pituitary body have been observed in the rat after irradiation of the testes.[46,86] In this process the interstitial tissue of the testes remains morphologically intact or even becomes hyperplastic. This suggests that the germinal epithelium or its derivatives may have an endocrine function. Further evidence is the appearance of "castration cells" in the pituitary body after ligation of the ductuli efferentes.[85]

The relative sensitivity to irradiation of the human ovary and testis has not as yet been finally established. No additional conclusive information was adduced on examination of tissues of patients exposed at Hiroshima and Nagasaki. The histologic changes were less spectacular in the ovary. The incidence of amenorrhea in the women was found to be inversely proportional to their distance from the center, but data of this type are less objective than sperm counts in the men and are somewhat obscured by the high incidence of "war amenorrhea"[47] in Japan, and perhaps by uterine bleeding of other than menstrual origin such as may accompany purpura. According to Dunlap,[22] the sterilizing dose for men is probably less than that for women. Under the conditions of irradiation described by Peck and his associates,[67] it was possible to produce permanent amenorrhea in 50 per cent of women following the administration to the tissues of 125 to 150 r. Above 625 r., almost all female patients were permanently castrated. It seems possible that nonfatal doses of radiation to the body as a whole may produce permanent sterility in some instances. On the other hand, even massive doses to the ovary may not result in permanent amenorrhea.[45] It is interesting to note, moreover, that conception can take place in some patients despite post-irradiation amenorrhea.[58] Species differences may exist in

the relative sensitivity of the gonads of the two sexes. Thus, in the mouse, Lorenz and his associates[53] found that upon protracted irradiation with small doses the injurious effect was cumulative and irreversible for the ovary but not for the testis.

### *The Fetus and the Germ Plasm*

It is now well known from clinical experience that irradiation may exert damaging effects on the unborn child without producing abortion. The resistance of the corpus luteum is well known.[73] After the application of a 60 per cent skin erythema dose (600 r. by his technic) to the tissue of the ovary, Mayer and his co-workers[58] found that abortion could be induced in 96 per cent of pregnant women. If an abortion does not result after large doses of radiation to the pelvis, the incidence of microcephaly and idiocy in a child is high, especially if the irradiation is administered before the end of the fourth month of pregnancy.[22] No statistics are available concerning such occurrences among the Japanese after the atomic bombings. The disrupted municipal facilities prevented accurate collection of vital statistics. It is probable that infant mortality was high because of the appalling hygienic conditions that prevailed after the atomic bombings and the great typhoons that followed.

Non-sterilizing irradiation of the female pelvis, when carried out before conception, is stated not to be followed by an unduly high incidence of abnormal offspring.[22,30,63,64] The studies concerning fertility made to date by questioning radiologists[42] or technicians[65] are inconclusive, since large masses of data are required together with adequate control material.

Effects on the germ plasm, as has been pointed out by the pioneer studies of Muller[61,62] on fruit flies, and by Snell[78] of Muller's laboratory on mice, must be studied with care over a series of generations before conclusive evidence can be forthcoming. These changes in the germ plasm are entirely distinct from those that can be produced in the embryo by radiating the products of conception. Muller[61] and others have demonstrated changes of two types in the germ plasm itself consequent upon irradiation: (1) gene mutations, by which is implied a change in the actual composition of the genes, and (2) chromosome transformation, whereby is implied a change in the position of the genes within the chromosomes. Such gene mutations as may result are usually recessive, and can be detected no sooner than in the third generation, and then only by inbreeding. Such mutations are more apt to be manifested by the elusive effects of lower "general vitality or efficiency than conspicuous

morphological abnormalities."[62] The most common situation, moreover, is for the gene or chromosome mutations to be lethal to the embryo. These fundamental facts were established for Drosophila by Muller and have been confirmed by others for many species. In mammals, Snell,[78] working with mice, found evidence of translocation changes in the chromosomes manifested by heritable lowered fertility ("semi-sterility"). Small litters developed in stocks the male ancestors of which had had their testes exposed to doses of between 600 and 800 r. Such heritable changes can be produced by irradiating mature spermatozoa as well as the spermatogonia, although a larger dose is needed to effect them in the latter.[62] All of these changes followed acute irradiation. Lorenz and his associates[53] could find no evidence of an effect on the germ plasm when minute doses of gamma rays were applied at low intensity over long periods to successive generations. The special sensitivity of the spermatozoa has stimulated Muller[61] to say that "it should, therefore, be mandatory for a man to abstain from acts of reproduction for some 2 months after his testes have been exposed to any considerable dose of radiation." Likewise the genetic consequences of mass irradiation on large populations have been considered recently by Muller[61] who has stated "if, as in flies, a total dose of 50 r. units, applied to the spermatozoa, results in a mutation frequency about equal to the natural mutation frequency, but added to it, and if this frequency is taken as being about one mutation in 10 to 20 germ cells, then I should hold the effect important." Thus, as the use of atomic energy becomes more and more widespread, the necessity of protecting populations becomes increasingly imperative, even considering the quantitative factors that have been discussed in the preceding paragraphs.

### *Neoplasia*

The existence of a very high incidence of deep burns involving large areas of skin would suggest that carcinoma arising in the epithelium covering the scars will be observed. It will be of interest to determine whether patients who had flash burns, and who consequently were exposed to intense ultraviolet radiation, will have a higher incidence than those whose burns were produced merely by contact with flame or hot objects. Whether the additional factor of exposure to gamma radiation will increase the incidence of carcinoma arising in the burned integument likewise remains to be determined.

Radiation dermatitis, whose precancerous nature has been described by Wolbach,[96] Saunders and Montgomery,[76] and others, was not found

among the survivors. An erythema dose to the skin as a whole would be fatal, especially if the soft rays responsible for the latter were mixed with more penetrating radiations.

Bone sarcomas in man have been described after radiation of benign tumors or even normal bone.[15] Large doses locally applied, however, appear to be required before tumors will result. Such doses again would be fatal if applied to the body as a whole. A much more palpable danger would exist from the ingestion or inhalation of radioactive material, as Martland[55] showed in the radium dial painters. Lisco, Finkel, and Brues[51] already have produced bone tumors experimentally with plutonium and radioactive fission products. In the patients subjected to the atomic bomb there was no evidence of the introduction of radioactive material.

Ovarian tumors have been produced in mice with remarkably small doses of gamma rays—as little as 50 r. given at one time, or 0.11 r. given daily for a total of 90 r.[44,53] The tumors—granulosa cell, tubular adenoma, or luteoma—appear after atrophy of the germ cells. Nothing comparable has as yet been observed in human pathology, but women exposed in the bombed cities should certainly be studied with care over a long period.

The evidence concerning the leukemogenic action of x-rays has been reviewed by Furth.[28] Chronic irradiation has repeatedly been proved to increase the incidence of leukemia in susceptible strains of mice.[40,53] Also, radiologists are known to have a death rate from leukemia greater than that of other physicians.[54] Relatively little is known about the effect of single doses of penetrating gamma rays. Furth concluded that x-rays are only weakly leukemogenic and then only after a long incubation period. There has not been an unduly high incidence of leukemia at Hiroshima and Nagasaki to date as far as can be determined,[91] and the single case of monocytic leukemia is considered purely adventitious. However, further observation will be necessary before this question is decided.

Little material is at hand by which any possible effect on the growing tissue of bone can be evaluated. In clinical experience, radiation possessing certain qualities and locally applied has been found to produce damage to the epiphysis without visible injury to the skin. Whether radiation of the intensity necessary to produce this effect is within the tolerance range when applied to the whole body remains to be determined by biometric and roentgenographic studies of surviving irradiated children of the Japanese cities.

## Summary and Conclusions

The explosion of the atomic bomb produced mechanical, thermal, and ionizing radiation injuries. The last were quantitatively the least important in the production of casualties.

Direct blast injuries analogous to those inflicted by high explosives were almost unknown among survivors, as indicated by an incidence of ruptured eardrums of about 1 per cent. Almost universal, however, was damage produced by flying glass and the falling beams of wooden houses. The more severe injuries were rare since those that had been severely hurt were killed by fires that swept the city before rescue operations could be instituted.

The burns among survivors were largely of the "flash" type, the result of an exceedingly large quantity of radiant heat acting for an exceedingly brief interval. The effects of exposure extended to approximately 4000 yds. from the bomb. Only survivors in the direct path of the rectilinear rays were involved, so that the burns were of a sharply outlined "profile" or "mask" type. Depigmentation at the center with marginal hyperpigmentation of the burns was prominent in patients close to the bomb, but at greater distances the entire exposed surface became intensely pigmented, and the pigment showed no tendency to fade within 4 months. There was histologic evidence that depigmentation occurred without destruction of the squamous epithelium of the surface, suggesting the action of specific wavelengths.

Even minor injuries and burns became serious foci of infection in persons who also suffered the leukopenia resulting from radiation.

The effects of ionizing radiations resembled closely those produced by total body x-irradiation of animals and men. A special effort was made to center the study of the lesions in patients who had sustained little or no other injury. The effects of ionizing radiations were observed in varying degrees of severity in poorly shielded patients who had been within approximately a mile from the bomb.

Nausea and vomiting occurred in many adequately exposed persons within a few hours after the bomb. The earliest autopsy material was from persons dying "mysteriously" with symptoms of severe diarrhea and fever on the third day after the bomb. In them, epilation and purpura had not had time to appear. After the end of the second week, however, these signs became manifest, and the infective complications of an aplastic anemia became increasingly prominent. Leukopenia had been observed within the first few days after the bombing. After the sixth week, the bone marrow tended to recover and the mortality de-

clined sharply, although an occasional patient succumbed to organizing pneumonitis or ulcerative enteritis. At necropsy, changes were found in the skin, gastro-intestinal tract, gonads, and hemopoietic tissues.

### *The Skin*

In a few cases there were suggestive epithelial changes at the margins of ulcerative lesions in patients dying in the third week, but since most persons who received more than an erythema dose over the whole body died during the first confused days when autopsies were extremely rare, little material was available for study. Epilation in both men and women usually began 14 to 20 days after the bomb. It involved chiefly the scalp in a distribution resembling that of ordinary baldness. Histologically, the mechanism appeared to be entirely analogous to that of the usual processes of loss and replacement of the hair, arrest of mitosis in the matrix, failure of differentiation of the internal root sheath with extrusion of old hair, and finally (some 2 months after irradiation) renewed differentiation of the internal root sheath with penetration of the new hair through the old external sheath to the surface.

### *Gastro-intestinal Tract*

Typical radiation changes were seen in the intestines of persons dying as early as the fourth day. These consisted of the appearance of bizarre cells, some with enormous nuclei possessing a coarse chromatin network and a large body of cytoplasm. Some cells were found in atypical mitosis and tripolar mitotic figures were observed. In one patient who died on the tenth day, the cytoplasm and nuclei of the squamous epithelial cells of the pharynx and tongue were remarkably swollen, and fragmentation of the nuclei was observed.

### *Gonads*

Even at the fourth day remarkable changes were found in the testes, with detachment of the germinal epithelium together with an increase in Sertoli cells. Toward the end of the first month, there was almost complete loss of germinal epithelium. After the fifth week the tubules began to display thickening of the basement membrane and there were hyaline deposits restricting the lumina of the interstitial blood vessels. There was questionable hyperplasia of the interstitial tissue after the end of the sixth week. Clinically, there was a remarkable decrease in the count of spermatozoa of patients who had been close to the bomb. How permanent this will be is at present unknown. "Castration cells" were found occasionally in the pituitary body.

Much less striking changes were observed in the ovary. A few primary follicles were in process of atresia. The most usual finding was that of the absence of developing follicles despite the persistence of primary follicles. The endometrium showed an absence of corpus luteum effect.

### *Lymphoid Tissues*

When first seen, after 3 days, there was a remarkable degree of atrophy of the lymphoid tissue, including those of the spleen, leaving nothing but the reticular skeleton. Beginning on the fifth day, however, large numbers of atypical mononuclear cells resembling lymphoblasts or Reed-Sternberg cells began to appear. These gradually decreased in number during the following 3 months and in a few instances secondary follicles had reappeared by the end of this time both in the spleen and lymph nodes.

### *Bone Marrow*

Even within the first week, in heavily irradiated individuals, almost all mature myeloid and erythroid tissue had disappeared, but there already was evidence of proliferative activity on the part of the reticulum cells. During the first month such proliferative activity became remarkable in many cases, but the products were largely atypical reticulum cells and plasma cells. In some patients, after various lengths of time, there was renewed differentiation into granulopoietic and erythropoietic tissue, and in some, who died toward the end of the sixth week, actual hyperplasia of this tissue was observed, although peripheral leukopenia had been noted.

After the sixth week more and more bone marrows tended to show hyperplasia of myeloid cells and the incidence of leukopenia decreased. In all of these marrows, however, considerable numbers of reticulum cells, plasma cells, and lymphocytes persisted in increased numbers. As the marrow recovered, polymorphonuclear leukocytes became numerous in the lesions and hemorrhage ceased to be an important factor. The important lesions at necropsy at this time were either a necrotizing pneumonia, sometimes in process of organization, or an ulcerative enteritis. Thrombocytopenia was at its lowest level at about the third to fourth week. Thereafter there was rapid recovery. Anemia also was severe during the third to fifth weeks in many patients, but in others it gradually reached its lowest levels thereafter. Recovery in these people was sluggish. This has been associated with dietary deficiency as well as with the effects of the ionizing radiation and of the infections that followed.

No defense has as yet been developed against the destructive effects upon cells subjected to massive amounts of ionizing radiations. Hope

for success in treatment lies in the remarkable resistance of the reticulum cell and the tendency of the marrow ultimately to recover. Pending the resurrection of the marrow, the main therapeutic problems are those of hemorrhage and infection. Despite recent advances, new and more efficient methods for meeting this double challenge remain to be discovered.

Among the many problems that are still to be investigated among the populations of Hiroshima and Nagasaki are: (1) Whether permanent damage of such nature as to reduce the life span was inflicted upon survivors who have apparently recovered. (2) Whether there will be an increased incidence of neoplasia (including leukemia) among the burned or irradiated patients. (3) Whether the growth of irradiated children has been impaired. (4) Whether permanent sterility was induced in any group of survivors. (5) Whether genetic changes will appear, as indicated by decreased fertility, or demonstrable anatomic or physiologic changes. These problems will require many years, or even generations for their solution, if they can be solved at all.

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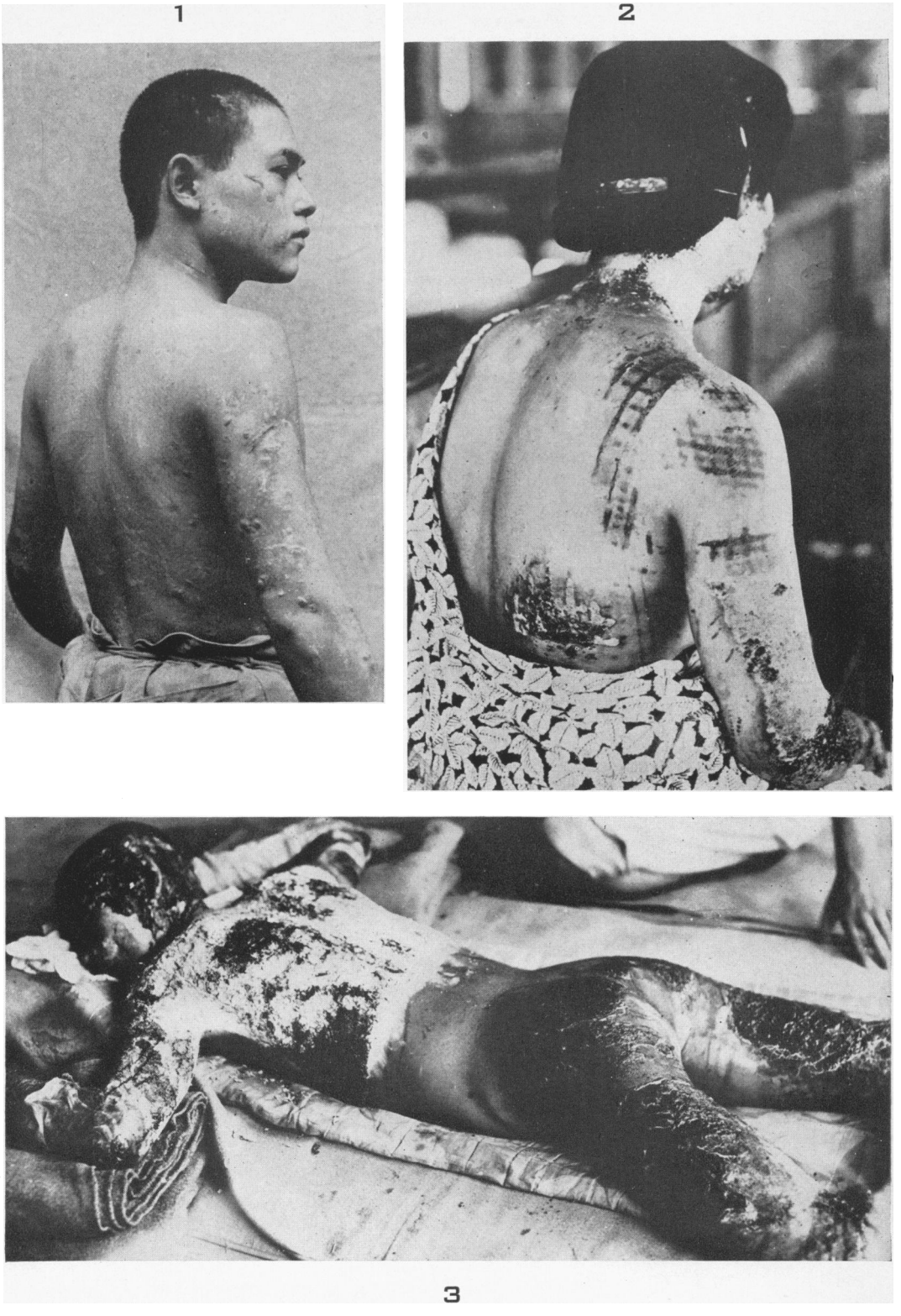
## DESCRIPTION OF PLATES

### PLATE 121

FIG. 1. Multiple injuries by flying glass. Patient was in a standing position, approximately 5 ft. from a window, indoors in a military barracks. Upper torso was nude but he was wearing trousers, which were not penetrated by the glass. Keloidal overgrowth of connective tissue. White blood cell count was 13,000 on the 44th day. Takatomi. Male, age unknown. Approximately 1000 yds. Died on the 57th day. Army Institute of Pathology negative no. HP 151A. Bunka-Sha photograph.

FIG. 2. "Flash burns." The darker portions of a striped pattern of cloth that the patient was wearing absorbed more heat and produced the gridiron burns of the skin. The arm below the sleeve line and the unprotected face were most severely burned. The burns are very sharply outlined. Ushio. Female, age unknown. Distance unknown. Late August, 1945, approximately 3 weeks after bombing. A.I.P. neg. HP 138-d. Photo made by Japanese medical officers of Tokyo 1st Military Hospital.

FIG. 3. "Flash burns" of third degree. No protection by the hair. Partial protection of the lower extremities by cloth trousers, and complete protection of skin of abdomen by the multiple layers of a cummerbund. Burns of the back, where there was no clothing, are sharply outlined. Name unknown. Male, age unknown. Distance unknown. A.I.P. neg. HP 142. Photo made by Japanese medical officers of Tokyo 1st Military Hospital.




Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 122

FIG. 4. "Flash burns." Depigmentation sharply outlined by pigmented tissue in a very narrow band. The line of the burn extends upwards on the chin. The darker material in the peri-aural region is not pigmented tissue, but is a crusted exudate and keratin. Kosugi. Female, 17 years of age. Approximately 1700 yds. 100th day. A.I.P. neg. HP 117 (K).

FIG. 5. "Flash burns." Deep chocolate-brown pigmentation. Very sharp outlines. Protection of upper portion of neck by shadow of mandible, and of nasolabial and lateral nasal grooves by the alae and nose. Enami. Male, 30 years of age. Approximately 2300 yds. 99th day. A.I.P. neg. HP 112b (K).

FIG. 6. Flash burns of skin. General view. Zone of greatest destruction of epithelium at the right. Depigmented tissue with relatively well preserved epithelium in central zone. Hyperpigmented tissue at left (see Figs. 11 and 12). K-4. Kume. Male, 32 years of age. Approximately 1000 yds. Died on the sixth day. A.I.P. neg. HM 134 (K). × 15.

FIG. 7. Keloids following flash burns. Protective effect of shoulder straps of slip and of sleeve seam. Pigmentation at margins of the burns. Akamatsu. Female, 21 years of age. Approximately 1400 yds. Approximately 2½ months. A.I.P. neg. HP 111-b (K).

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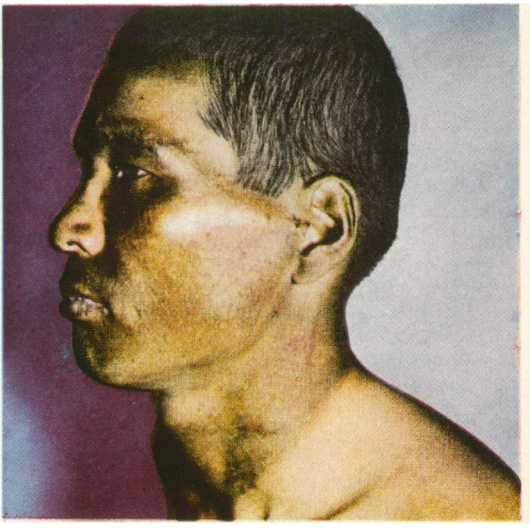

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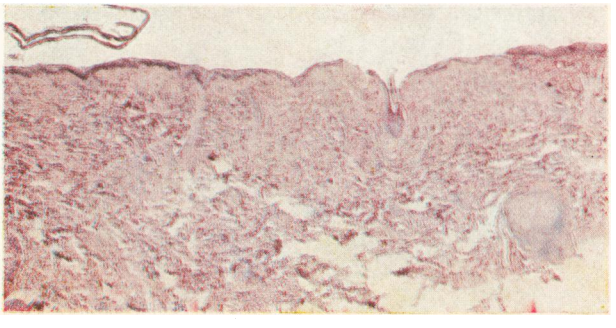

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Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 123

FIG. 8. "Flash burns" of shoulder. Mottled depigmentation of central portions where burn was most severe, outlined by a band of hyperpigmented tissue. There is a narrow zone of depigmentation between the normal and burned skin. Maeda. Male, 40 years of age. Approximately 2300 yds. 99th day. A.I.P. neg. HP 115-a (K).

FIG. 9. Epilation of scalp. Scattered long hairs of the original growth remain. Patient was inside a wooden building at Nagasaki at the time of the bombing. Epilation began on the 19th day, 3 days after the appearance of purpura. Leukopenia persisted for 2 months, but the patient recovered. 63rd day. A.I.P. neg. NP 159.

FIG. 10. Group II. Petechiae of epicardium. K-28. Kawaura. Male, 23 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HS 307 (K).

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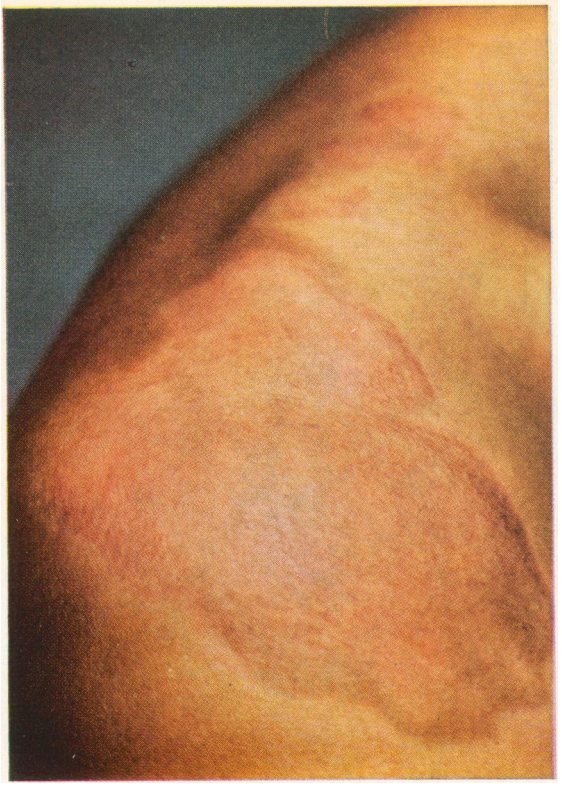

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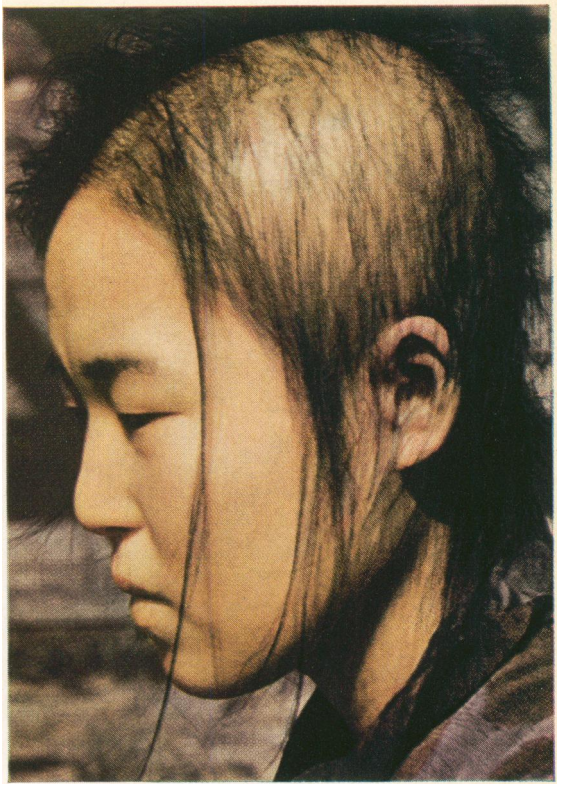

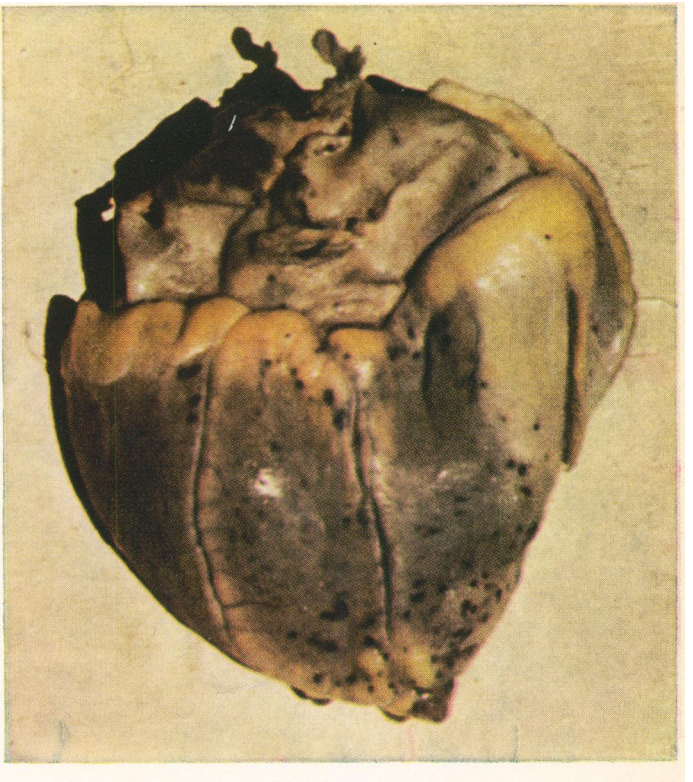

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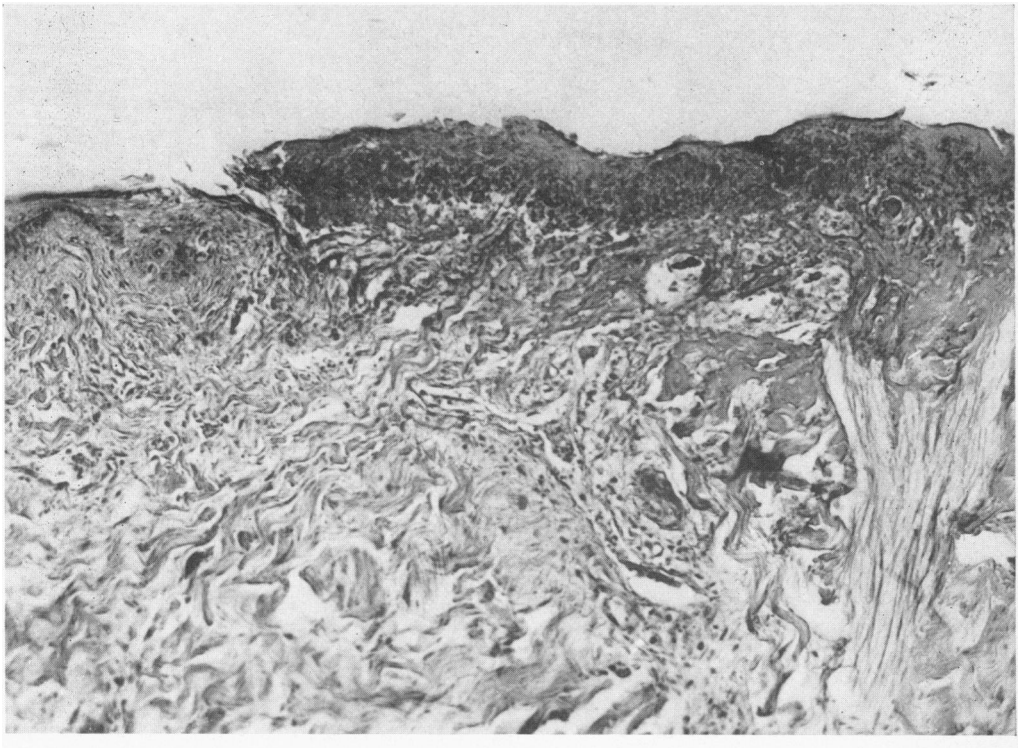
PLATE 124

FIG. 11. Group I. Enlargement of right-hand portion of Figure 6. At right, necrosis of epithelium; infiltration with large mononuclear elements, which also are in process of necrosis. At left, well preserved epithelium without pigment. Dermal melanophores also are not seen here. A.I.P. neg. HM 133. × 100.

FIG. 12. Group I. Enlargement of left-hand margin of Figure 6. Hyperpigmentation of skin. Large numbers of stellate melanophores among the epithelial cells. A.I.P. neg. HM 132. × 200.



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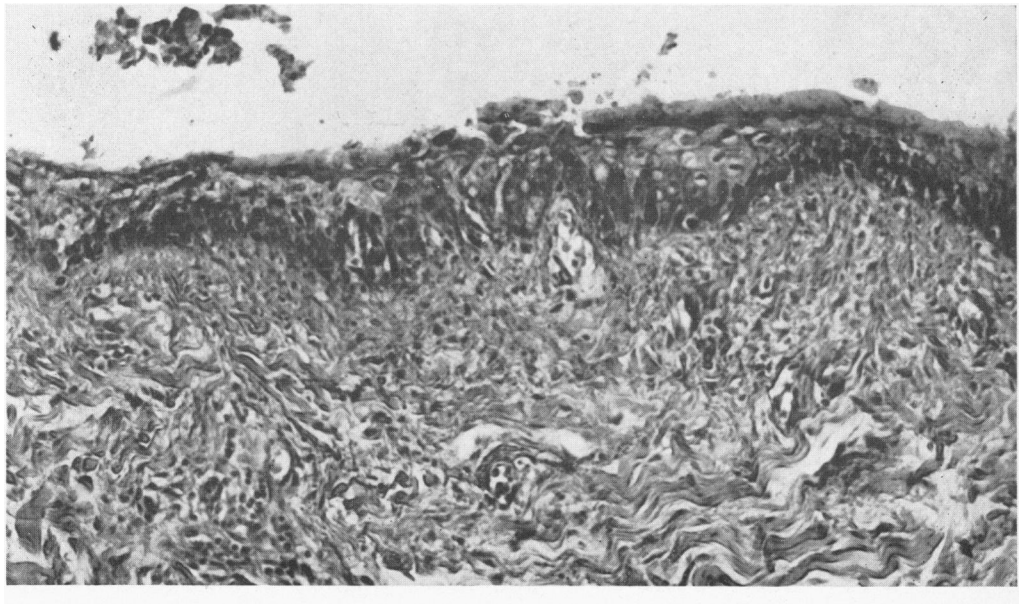

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PLATE 125

FIG. 13. Group I. Skin from burned area. Necrosis of epithelium and outer layers of derma. Bacterial masses in derma without cellular reaction. Vacuolation and shrinkage of acinar epithelium of sweat glands. Squamous metaplasia of duct of sweat gland. Bacterial mass within arrector pili muscle. K-5. Yano. Male, 39 years of age. Approximately 1000 yds. Died on the sixth day. A.I.P. neg. HM 130. × 50.

FIG. 14. Group I. Skin from burned area. Minute thrombus in blood vessel where wall has undergone necrosis. The exudate is almost exclusively of large mononuclear cells. K-3. Sakuma. Male, 15 years of age. Approximately 1000 yds. Died on the fifth day. A.I.P. neg. HM 113. × 350.

FIG. 15. Group I. Subcutaneous tissue deep to burn. Edema and myxomatous change of connective tissue. Proliferation and swelling of histiocytic and fibroblastic elements. Many mast cells are seen. From the same patient as Figure 14. A.I.P. neg. HM 118. × 100.

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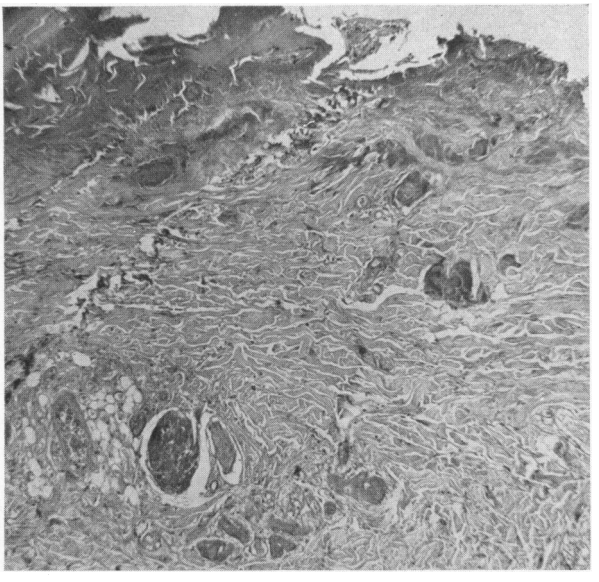

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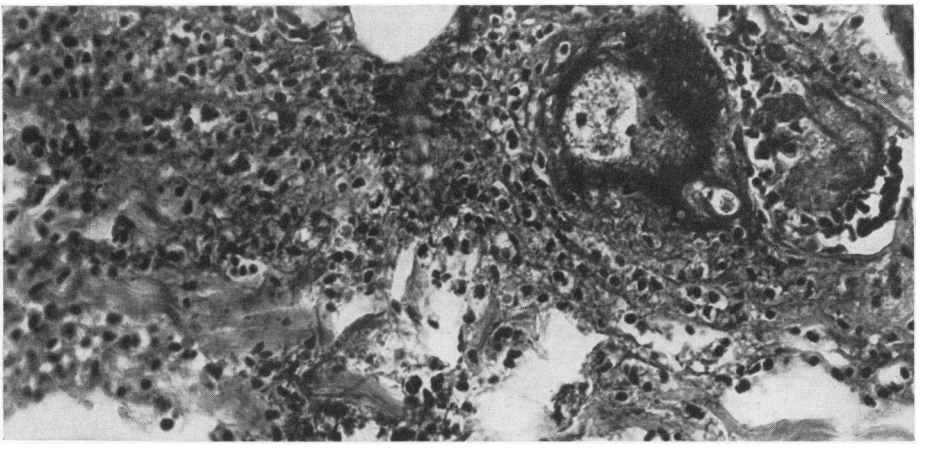

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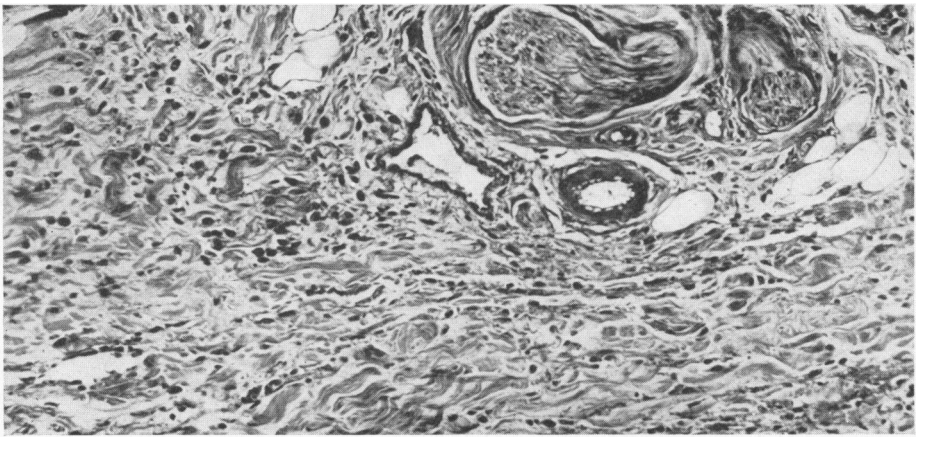


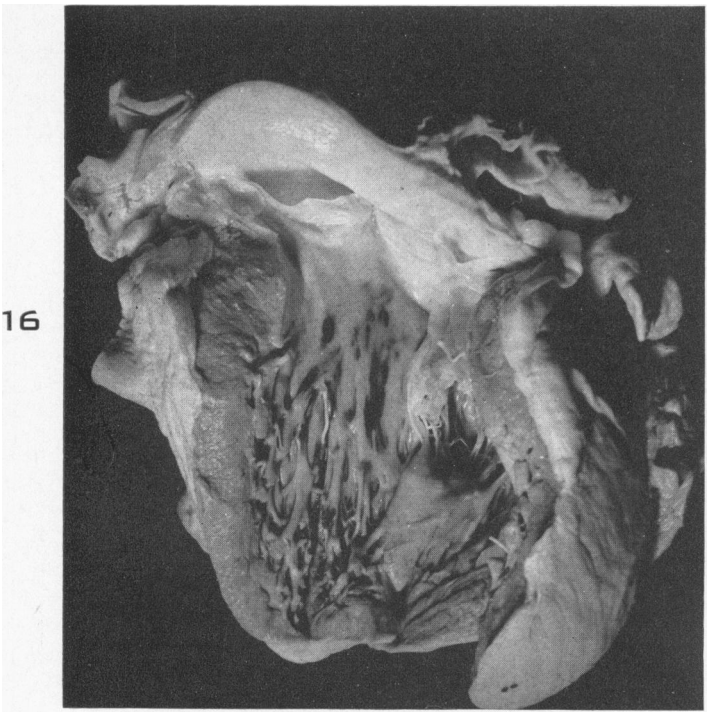
PLATE 126

FIG. 16. Group II. Subendocardial hemorrhages of left ventricle in region of conduction bundle. K-43. Horinouchi. Male, 33 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HS 326b.

FIG. 17. Group II. Focal necrotizing bronchiolitis and focal necrotizing neutropenic pneumonia with surrounding hemorrhage. Relatively more necrosis than in Figure 19. K-36. Morita. Female, 21 years of age. Approximately 1000 yds. Died on the 28th day. A.I.P. neg. HS 319.

FIG. 18. Group II. Lung. Scar of apex. Disseminated caseous tubercles surrounded by hemorrhagic parenchyma. K-40. Motoyama. Male, 29 years of age. Approximately 1000 yds. Died on the 30th day. A.I.P. neg. HS 322.

FIG. 19. Group II. Lung. Focal necrotizing bronchiolitis and focal pneumonia with surrounding hemorrhage. The foci of necrosis are minute. K-44. Araki. Male, 22 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HS 329.



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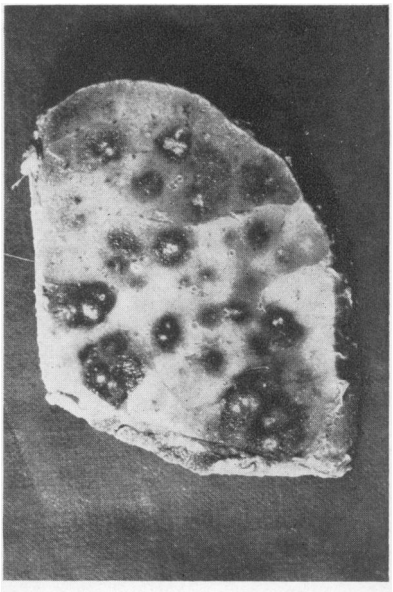

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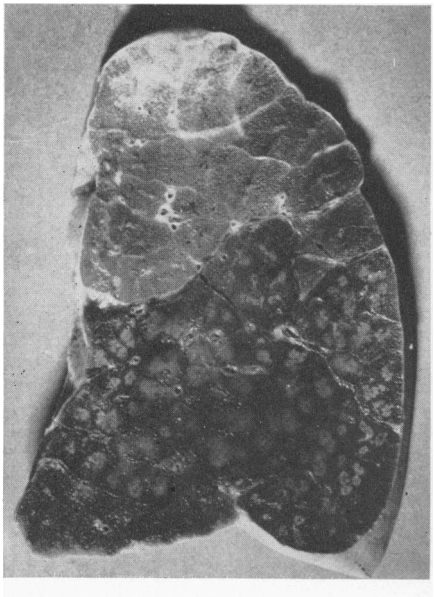

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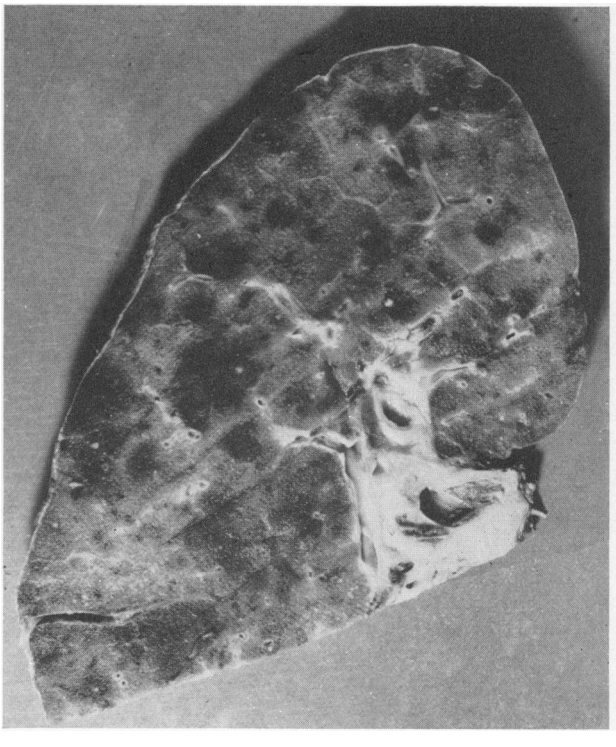

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PLATE 127

FIG. 20. Group I. Lung. Focal emphysema and atelectasis. Edema of pleura. K-1. Harada. Male, 13 years of age. Approximately 1300 yds. Died on the third day. A.I.P. neg. HM 104.

FIG. 21. Group II. Heart. Perivascular and interstitial infiltration with small and large mononuclear cells and plasma cells. K-29. Murakami. Male, 22 or 24 years of age (variously stated). Approximately 1000 yds. Died on the 27th day. A.I.P. neg. HM 154. × 220.

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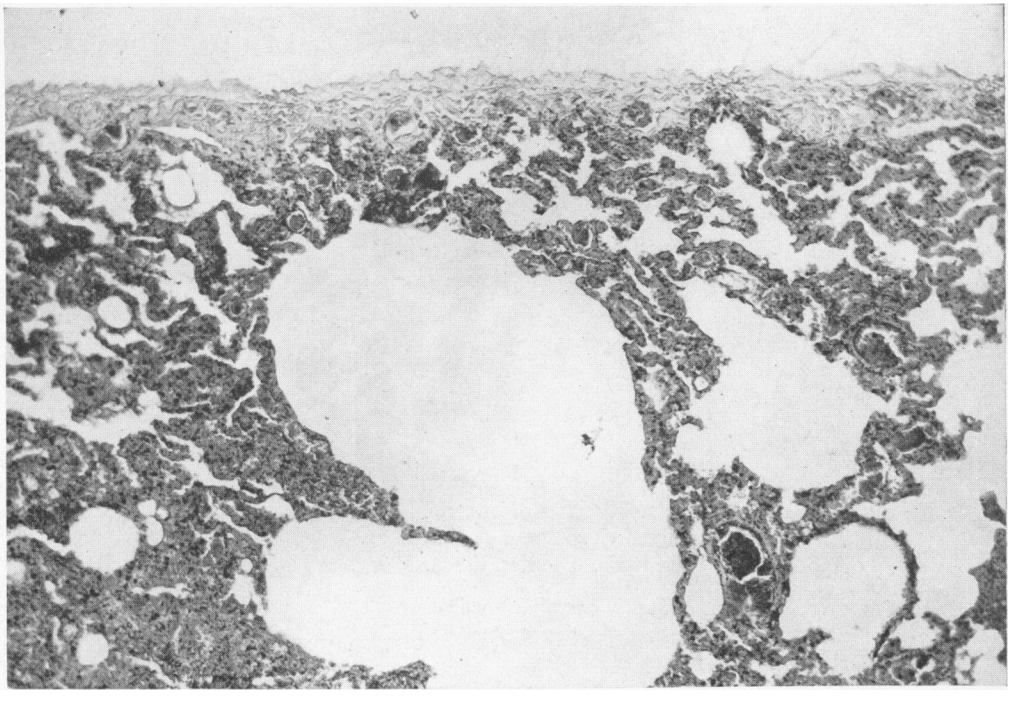

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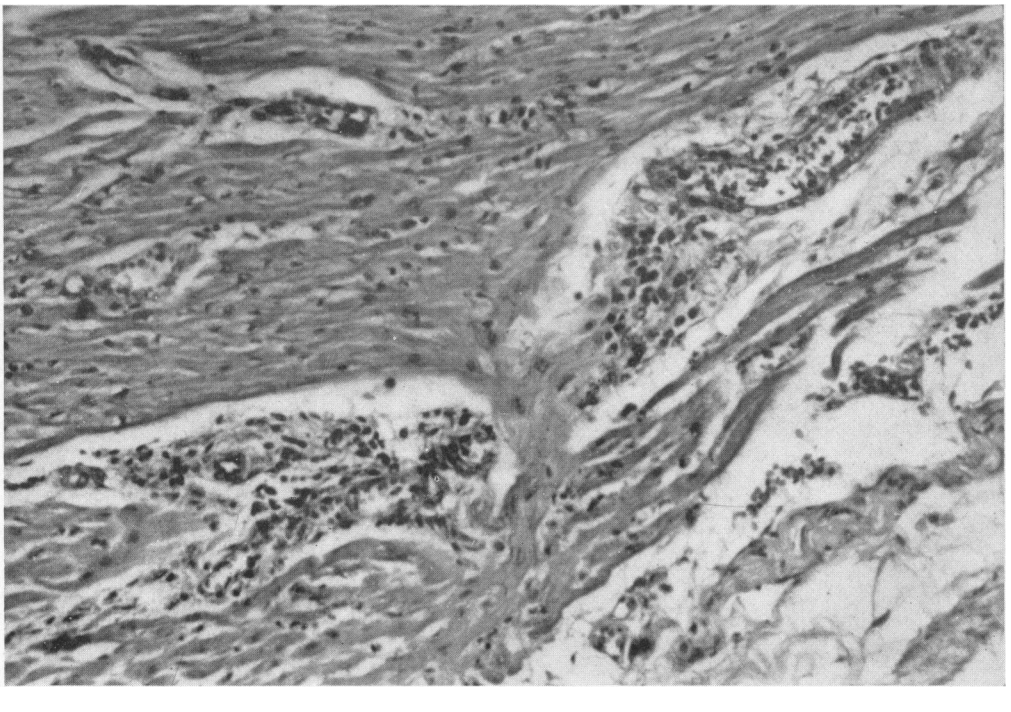

Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 128

FIG. 22. Group II. Lung. Necrosis of bronchiole. Bacterial masses attached to wall. Necrotizing and hemorrhagic pneumonia. K-21. Iseoka. Male, 45 years of age. Approximately 1000 yds. Died on the 24th day. A.I.P. neg. HM 145. × 100.

FIG. 23. Group II. Lung. Focus of "necrotizing and hemorrhagic aplastic pneumonia." Bacterial masses near center of the lesion. Lining membrane of bronchiole near right center of lesion is completely necrotic. K-47. Naka. Female, 35 years of age. Approximately 800 yds. Died on the 18th day. A.I.P. neg. HM 242. × 50.

FIG. 24. Group II. Lung. Edema of pleura. Necrotizing and hemorrhagic "aplastic pneumonia." K-119. Nagado. Female, 26 years of age. Approximately 1300 yds. Died on the 23rd day. A.I.P. neg. HM 288. × 115.

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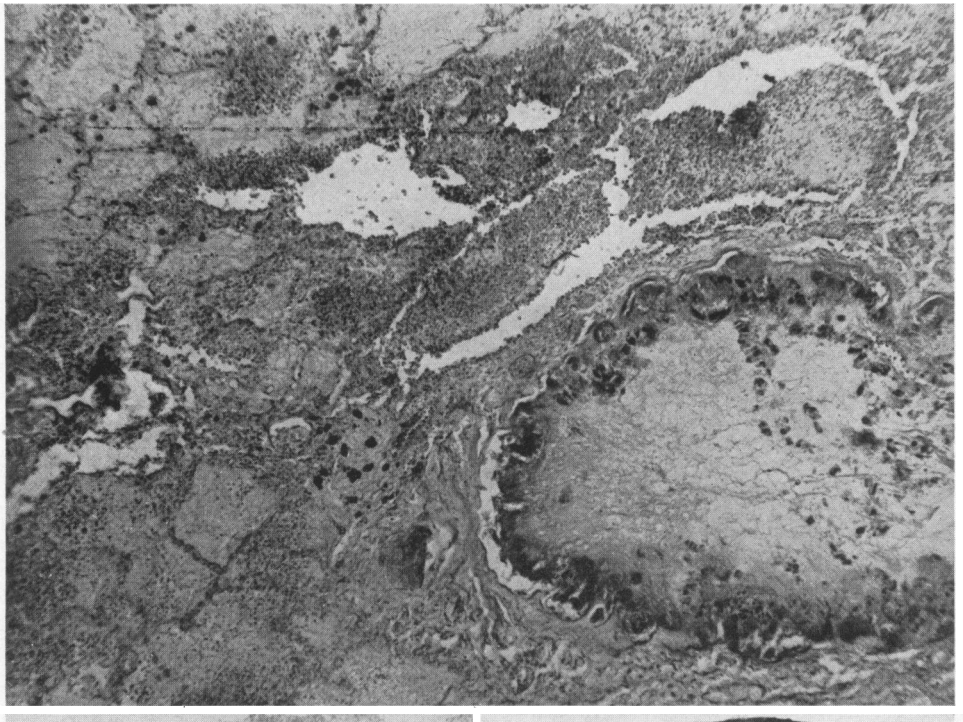

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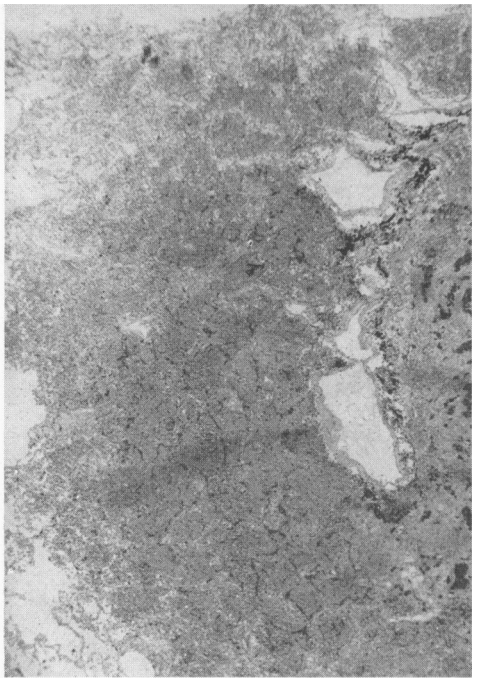

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Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 129

FIG. 25. Group III. Fibrous wall of abscess cavity. From the same patient as Figure 27. A.I.P. neg. HM 269. × 50.

FIG. 26. Group III. Lung. Organizing pneumonia. K-96. Sakoda. Male, 33 years of age. Approximately 1000 yds. Died on the 97th day. A.I.P. neg. HM 278. × 130.

FIG. 27. Group III. Right lung. Gangrene of upper lobe with sequestrated lung tissue. Abscess cavity in lower lobe. Diffuse necrotizing and organizing pneumonia. K-50. Kijima. Male, 31 years of age. Approximately 1000 yds. Died on the 100th day. A.I.P. neg. HS 333.

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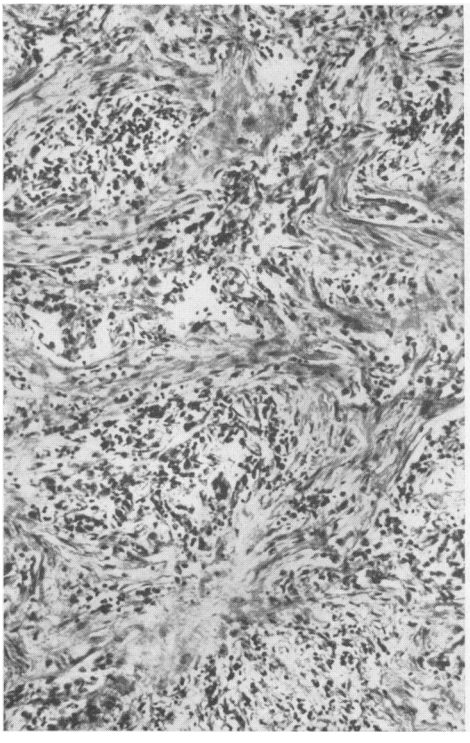

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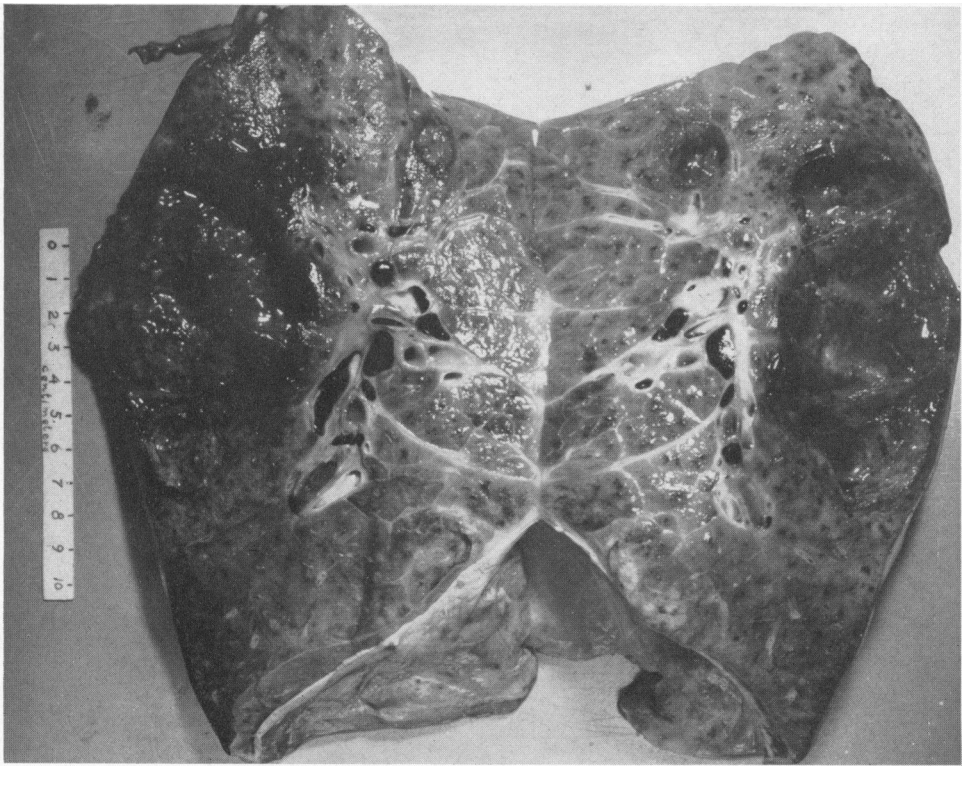
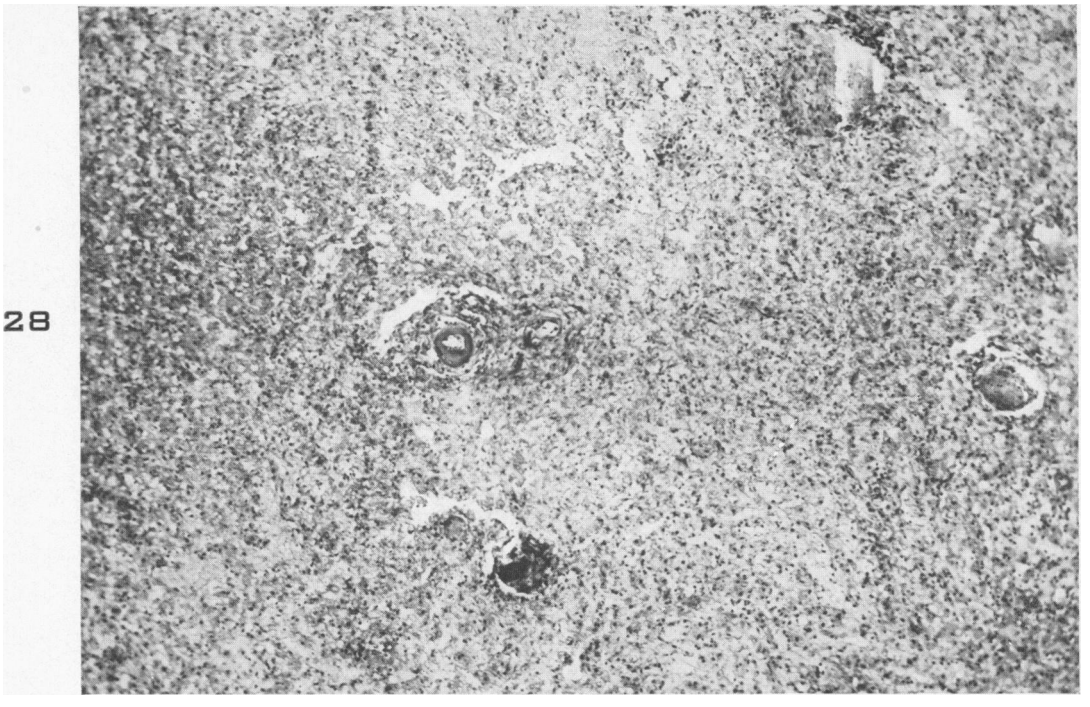


PLATE 130

FIG. 28. Group I. Spleen. Marked shrinkage of malpighian body. Disappearance of lymphocytes and of cells of Billroth's cords. Acidophilic refractile material in subendothelial position of central vessel. K-2. Onishi. Male, 24 years of age. Approximately 800 yds. Died on the fourth day. A.I.P. neg. HM 102. × 100.

FIG. 29. Group I. Spleen. Disappearance of lymphocytes from sites of malpighian corpuscles. Necrosis *in situ* of lymphocytes and of cells of germinal center. Acidophilic refractile material in subendothelial tissues of central arteries. From the same patient as Figure 28. A.I.P. neg. HM 100. × 400.



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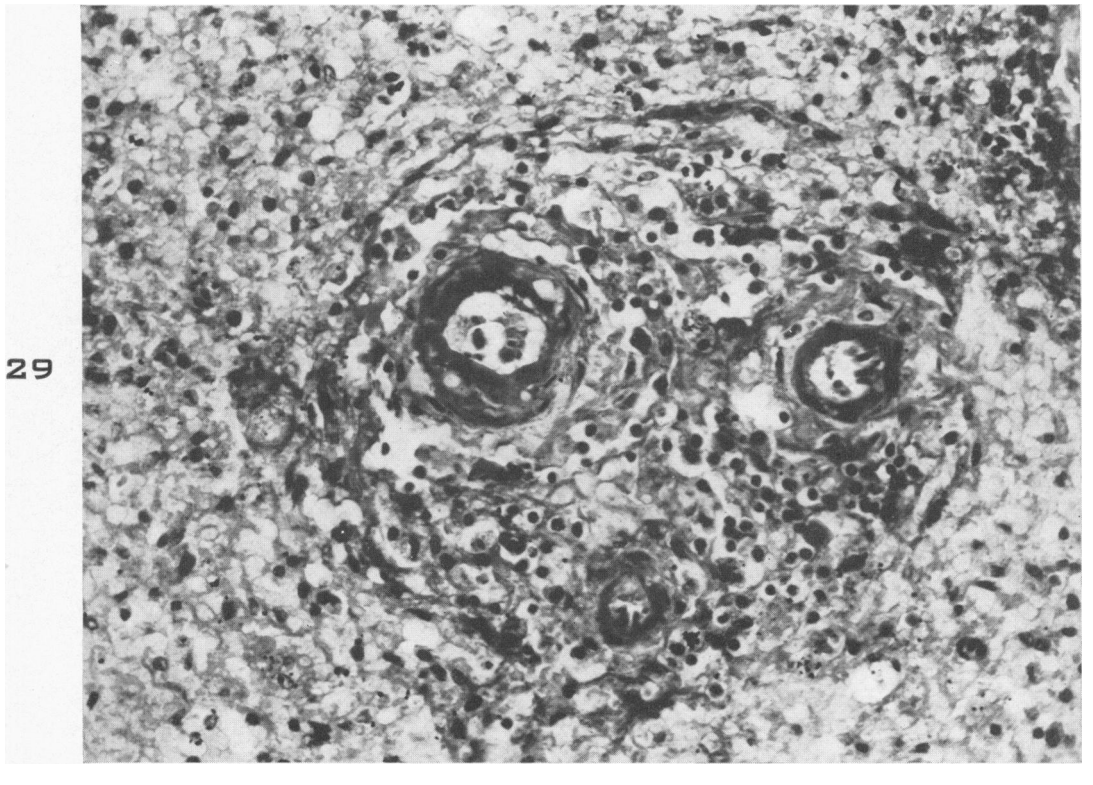

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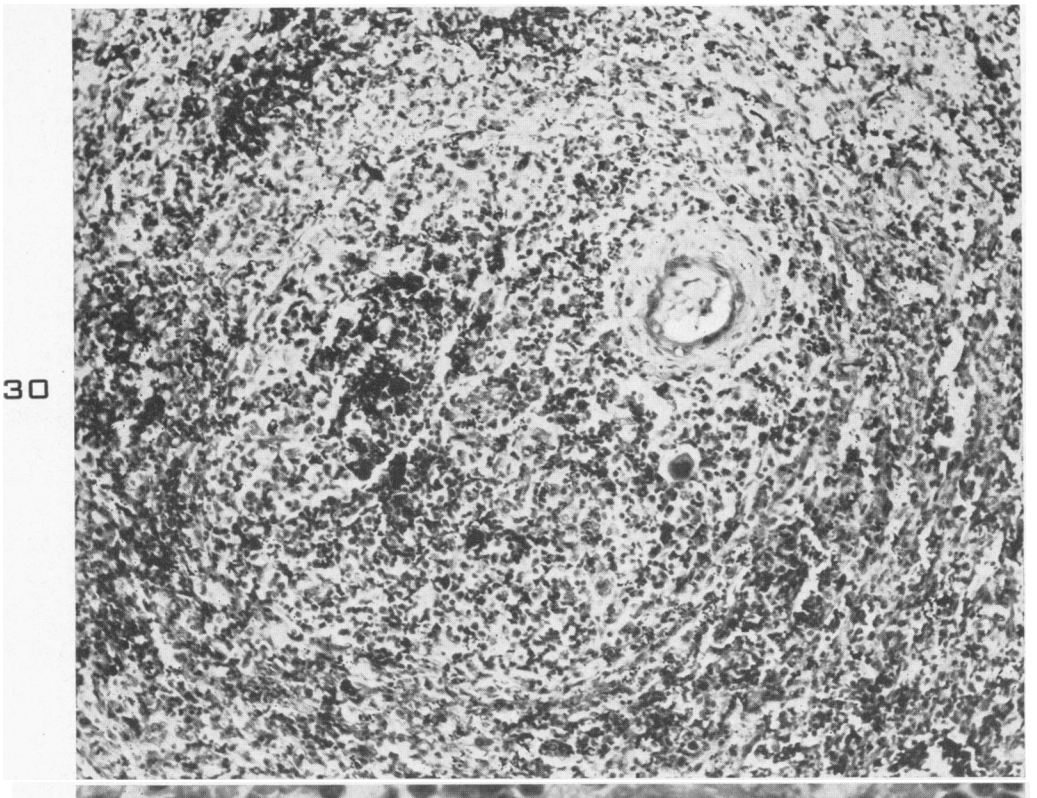
Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 131

FIG. 30. Group I. Spleen. Malpighian corpuscle. Paucity of lymphocytes. Giant cell resembling Reed-Sternberg cell. Hemorrhage in and about malpighian follicle. K-3. Sakuma. Male, 15 years of age. Approximately 1000 yds. Died on the fifth day. A.I.P. neg. HM 107. × 165.

FIG. 31. Group I. Spleen. Erythrophagocytosis. Atypical large mononuclear cells. From the same patient as Figure 30. A.I.P. neg. HM 120. × 750.



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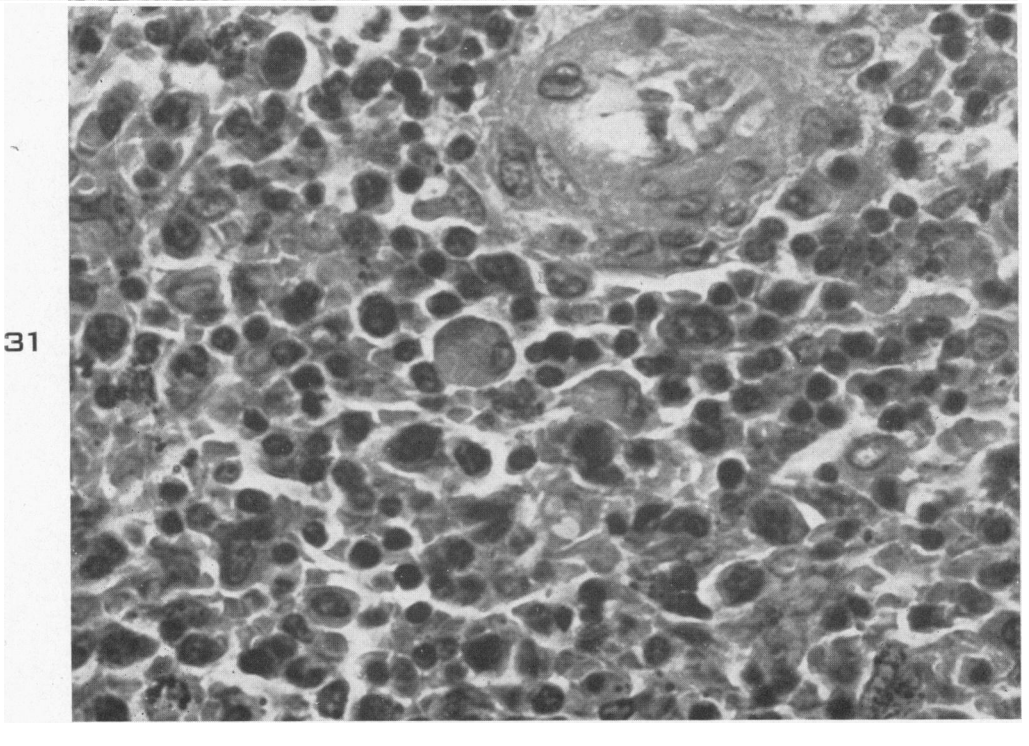

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PLATE 132

FIG. 32. Group I. Spleen. Knot of reticulum cells at center. Large atypical mononuclear elements. Group of minute nuclei. From the same patient as Figure 30. A.I.P. neg. HM 121 (K). × 350.

FIG. 33. Group II. Lymph node. Almost total disappearance of lymphocytes. Skeleton of reticular cells. Numerous mast cells. Giemsa's stain. K-28. Kawaura. Male, 23 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 295. × 500.

FIG. 34. Group III. Femur. Red gelatinous and gray-red cellular marrow in upper portion of shaft. Gelatinous and fatty yellow marrow in distal portion of the bone. From the same patient as Figure 70. A.I.P. neg. HS 334 (K).

FIG. 35. Group I. Marrow from long bone. Reticulum cells, plasmacytoid elements, and some large cells intermediate in appearance between the two. No normal hemopoietic tissue. Erythrophagocytosis by some of the reticular elements. This is the earliest histologic specimen of bone marrow available. By the criteria employed in the text it would be classified "type A," marked hypoplasia. K-5. Yano. Male, 39 years of age. Approximately 1000 yds. Died on the sixth day. A.I.P. neg. HM 131. × 650.

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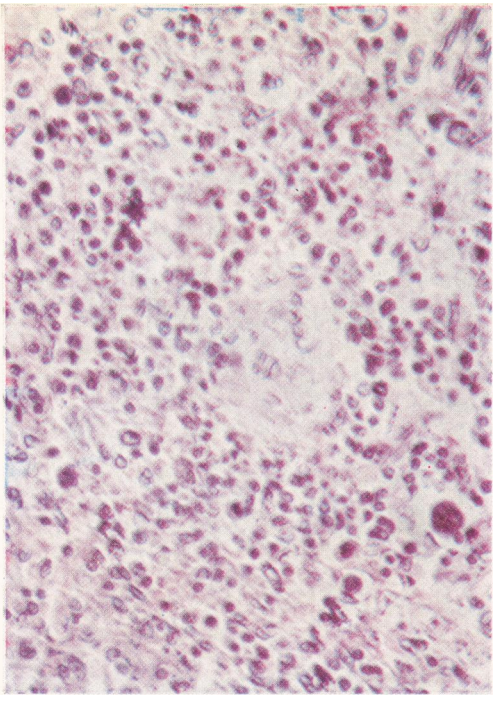

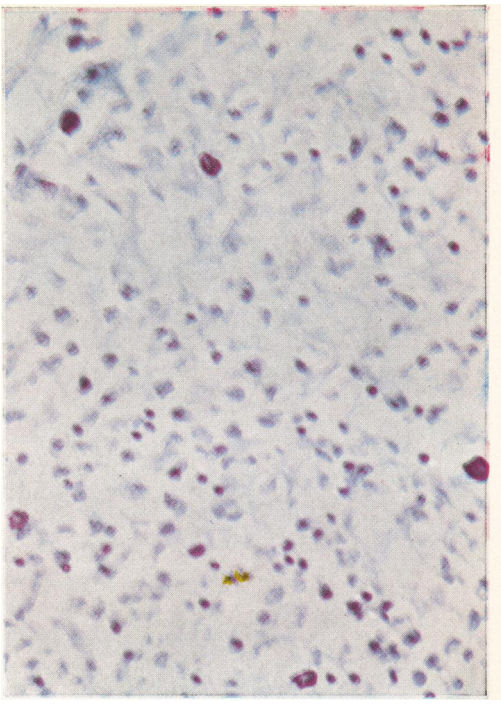

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Liebow, Warren, and DeCoursey

Pathology of Atomic Bomb Casualties

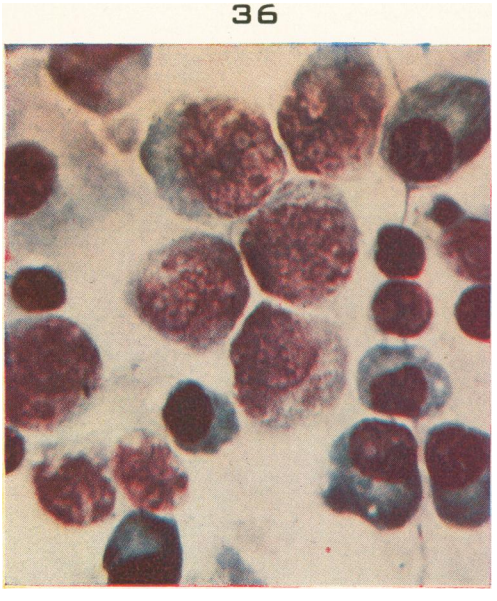
PLATE 133

FIG. 36. Group II. Smear of bone marrow. Reticulum cells, myelocytes with azurophilic granules, and cells transitional between the two. These transitional forms suggest a direct origin of myelocytes from reticulum cells in these rapidly regenerating marrows. Numerous plasma cells and forms transitional between them and the reticulum cells. Blast cells are rare in this smear. Wright-Giemsa stain. K-43. Horinouchi. Male, 33 years of age. Approximately 1000 yds. Died on the 32nd day. A.I.P. neg. HM 320 (K). × 800.

FIG. 37. Group II. Pituitary body. Vacuolated large basophilic cells ("castration cells"). Hyperplasia of basophilic cells. K-42. Moriseko. Male, 27 years of age. Approximately 1000 yds. Died on the 31st day. A.I.P. neg. HM 298. × 400.

FIG. 38. Group III. Scalp. Atrophy of hair follicles and associated sebaceous glands. There is no notable change in the sweat glands. For details see Figure 141. K-14. Yamamoto. Male, 25 years of age. Approximately 1000 yds. Died on the 47th day. A.I.P. neg. HM 280 (K). × 22.

FIG. 39. Group III. Testis. Disappearance of germinal epithelium and its derivatives. Thickening of basement membranes of the tubules by deposition of finely fibrillar collagenous material within the old basement membrane. Deposits of refractile acidophilic material beneath the endothelium of the blood vessels in the interstitium. K-14. Yamamoto. Male, 25 years of age. Approximately 1000 yds. Died on the 47th day. A.I.P. neg. HM 211. × 115.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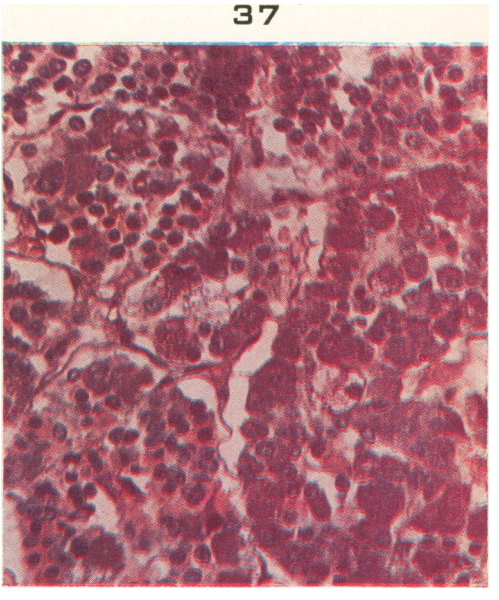
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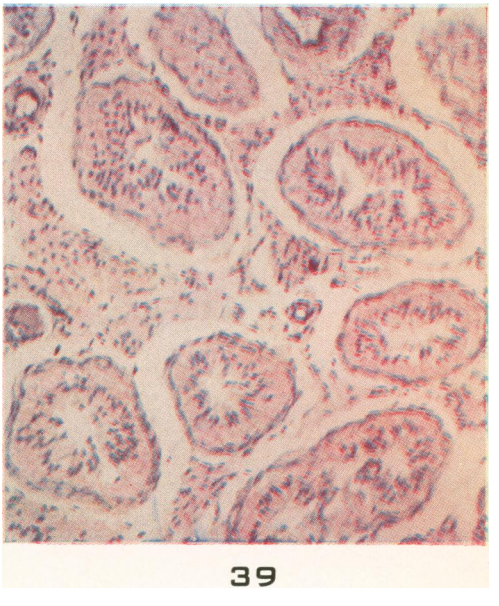
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PLATE 134

FIG. 40. Group I. Spleen. Tissue in neighborhood of central arteriole. Only rare lymphocytes are present. Numerous large atypical mononuclear elements, some in mitosis. K-9. Sakamoto. Male, 25 years of age. Approximately 1500 yds. Died on the eighth day. A.I.P. neg. HM 138. × 400.

FIG. 41. Group II. Spleen. Condensation of reticulum cells about central arteries of malpighian corpuscles. K-35. Takahashi. Male, 31 years of age. Approximately 1000 yds. Died on the 28th day. A.I.P. neg. HM 223. × 120.

FIG. 42. Group II. Spleen. Malpighian corpuscle. Almost total disappearance of typical lymphocytes. A few small and large plasmacytoid elements remain. Deposition of hyaline, homogeneous, acidophilic, refractile material beneath endothelium of central arteriole. Slight, if any, evidence of proliferative activity of the reticulum cells. K-47. Naka. Female, 35 years of age. Approximately 800 yds. Died on the 18th day. A.I.P. neg. HM 247. × 135.

FIG. 43. Group II. Spleen. Atrophy of lymphoid tissue. Atypical large mononuclear elements. Hyaline changes in walls of central arteries. K-121. Sakanishi. Male, 45 years of age. Approximately 1000 yds. Died on the 24th day. A.I.P. neg. HM 306. × 400.

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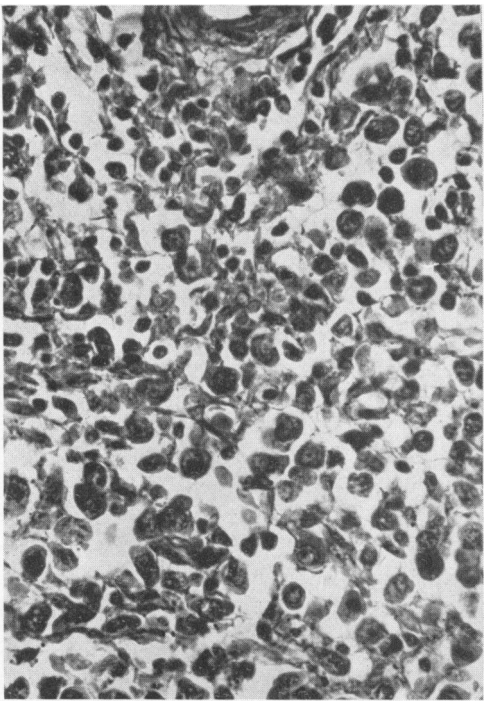

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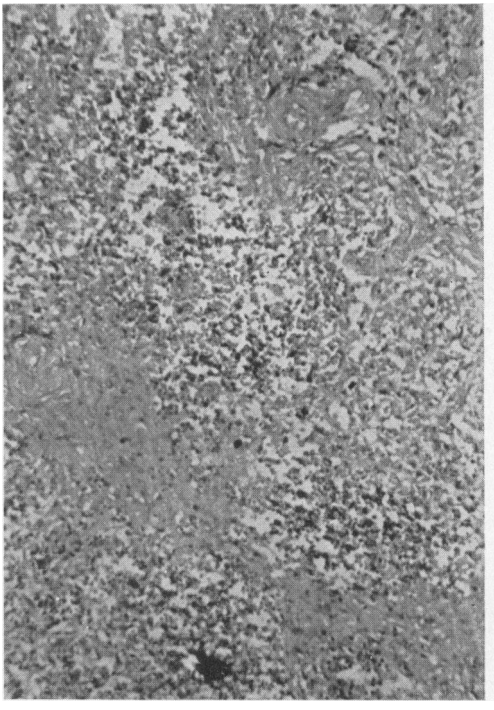

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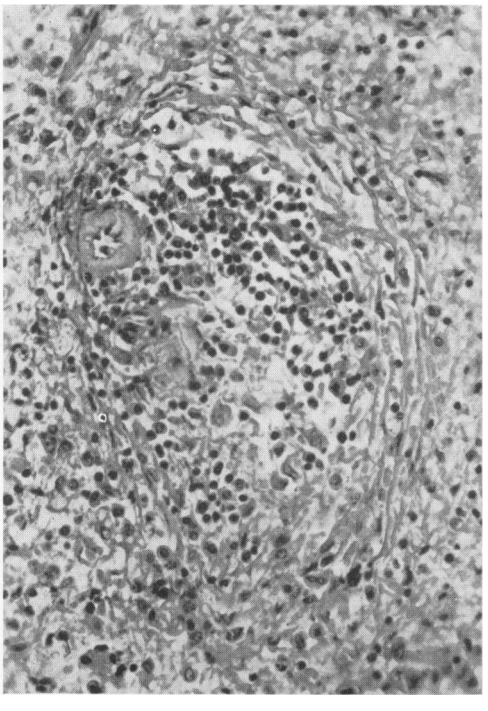

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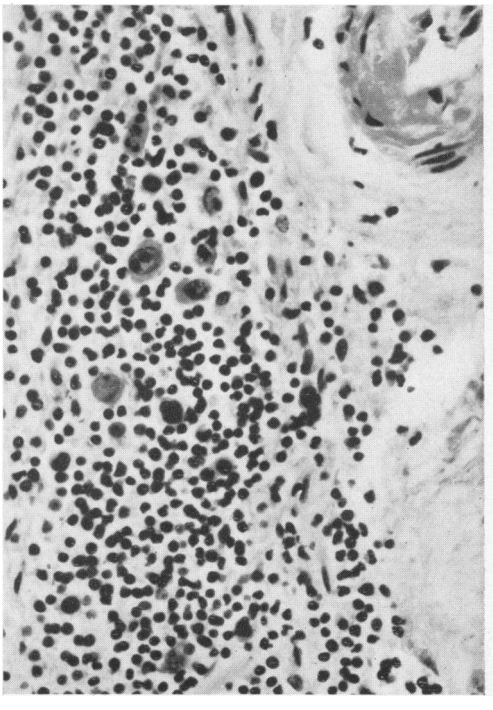


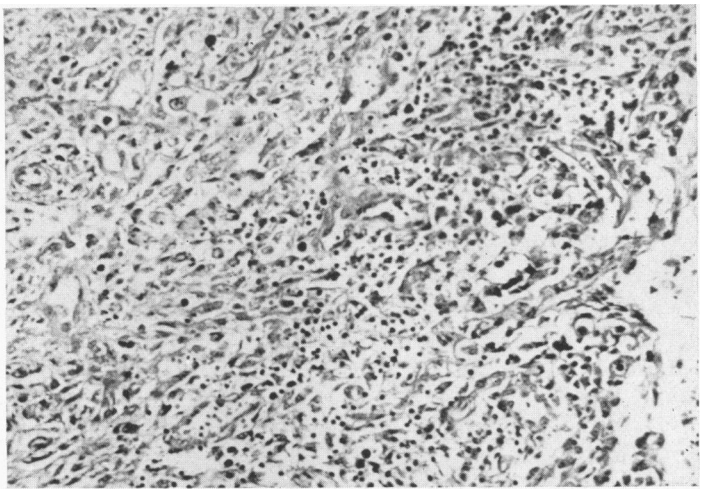
PLATE 135

FIG. 44. Group I. Lymph node. Collapsed reticular skeleton supporting a very few mature lymphocytes. K-98. Tamai. Male, 19 years of age. Distance unknown. Died on the tenth day. A.I.P. neg. HM 282. × 160.

FIG. 45. Group II. Spleen. Condensation of syncytial masses of reticulum cells about a regenerating malpighian corpuscle. Giemsa's stain. From the same patient as Figure 41. A.I.P. neg. HM 224. × 235.

FIG. 46. Group II. Spleen. Condensation of syncytial reticulum cells at margin of regenerating malpighian corpuscle. Giemsa's stain. Enlargement of a portion of Figure 45. A.I.P. neg. HM 225. × 400.

44



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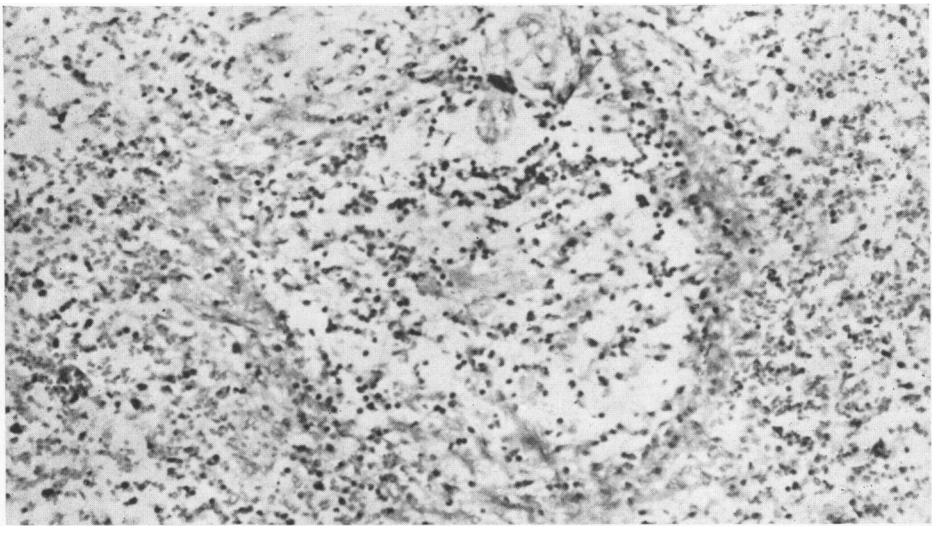

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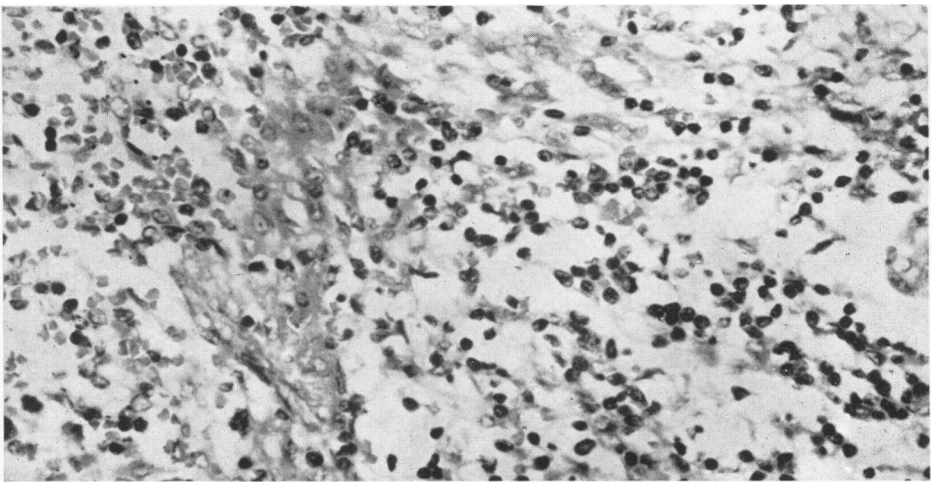


PLATE 136

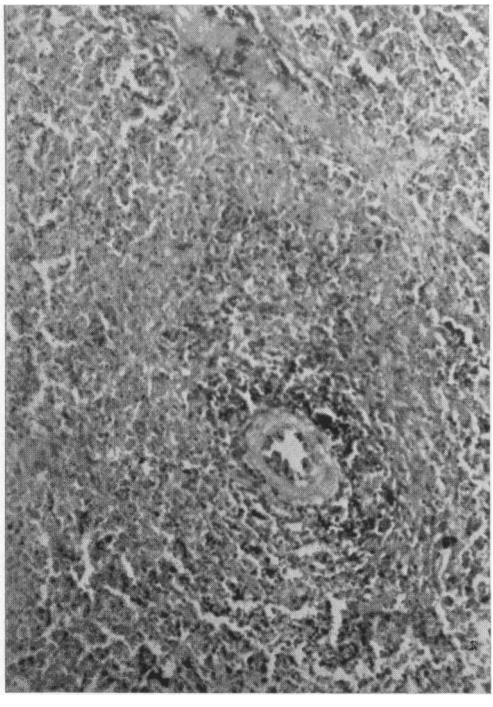
FIG. 47. Group II. Spleen. Condensation of syncytial reticulum at periphery of regenerating malpighian corpuscle. Beginnings of germinal center. K-38. Kamihara. Male, 22 years of age. Approximately 1000 yds. Died on the 29th day. A.I.P. neg. HM 226. × 145.

FIG. 48. Group III. Spleen. Germinal center in malpighian corpuscle. K-50. Kijima. Male, 31 years of age. Approximately 1000 yds. Died on the 100th day. A.I.P. neg. HM 267. × 200.

FIG. 49. Group II. Lymph node. Absence of germinal centers. Mature small lymphocytes are few. Numerous large lymphocytes, cells with the structure of lymphoblasts, and some elements intermediate in appearance between these and the elements of the reticulum. K-104. Yoshitomi. Male, 14 yrs. of age. Approximately 1000 yds. Died on the 21st day. A.I.P. neg. HM 286. × 115.

FIG. 50. Group II. Lymph node. Enlargement of a portion of Figure 49. A.I.P. neg. HM 285. × 400.

47



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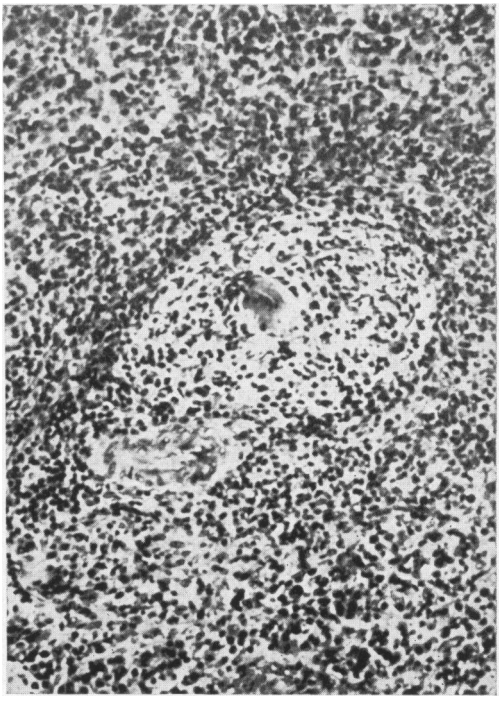

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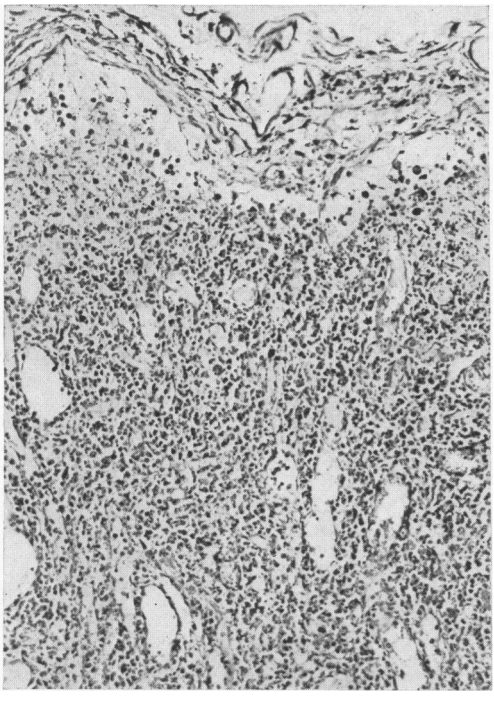

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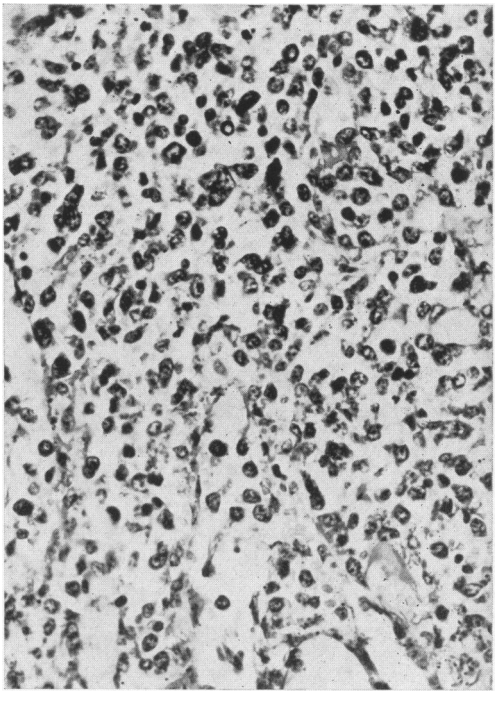


Liebow, Warren, and DeCoursey

Pathology of Atomic Bomb Casualties

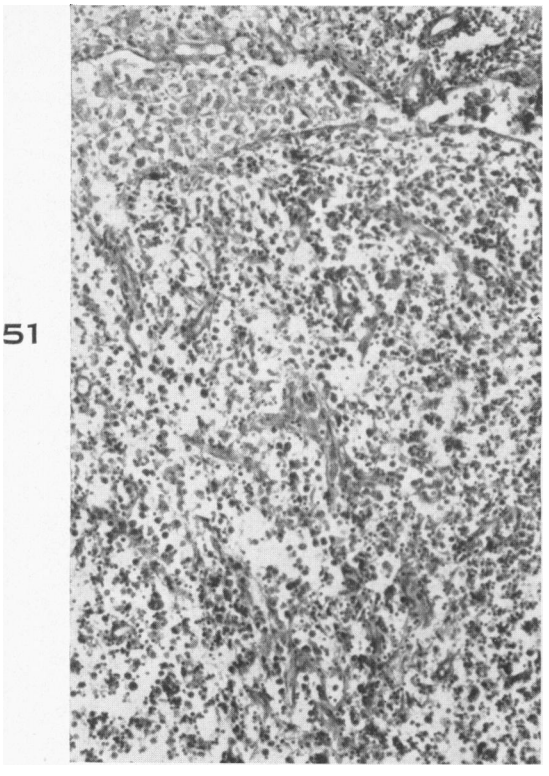
PLATE 137

FIG. 51. Group II. Lymph node. General view. Absence of secondary follicles. Very few small lymphocytes remain. Numerous plasma cells and larger cells intermediate in appearance between them and the elements of the reticulum. Large mononuclear cells with vacuolated cytoplasm in peripheral sinusoid. Thickening of capsule by granulation tissue. K-30. Nagashima. Male, 23 or 28 years of age (variously stated). Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 213. × 120.

FIG. 52. Group II. Lymph node. Enlargement of a portion of Figure 51, including a subcapsular sinusoid and the underlying parenchyma. A.I.P. neg. HM 214. × 430.

FIG. 53. Group II. Lymph node. Tissue near edge of focus of necrosis. Large mononuclear elements with folded nuclei, probably atypical reticulum cells. Occasional plasma cells. Hemorrhage. K-28. Kawaura. Male, 23 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 152. × 450.

FIG. 54. Group III. Lymph node. Enormous atypical cells resembling Reed-Sternberg cells. K-82. Oku. Female, 15 years of age. Approximately 1200 yds. Died on the 42nd day. A.I.P. neg. HM 301. × 400.



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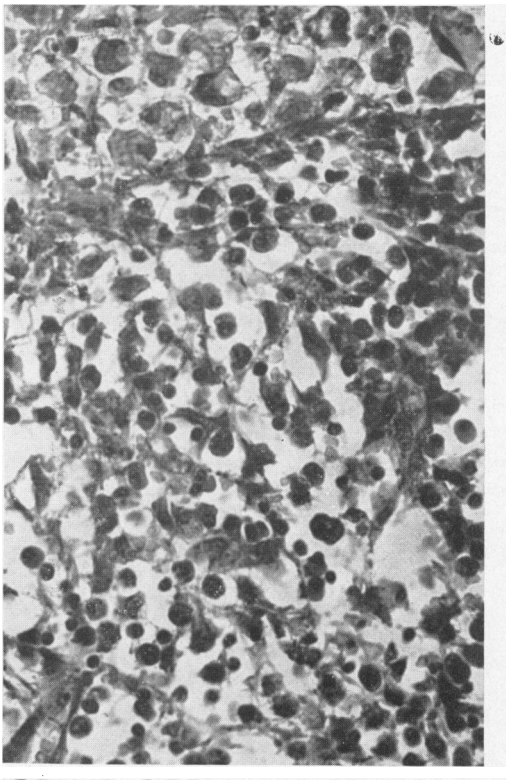

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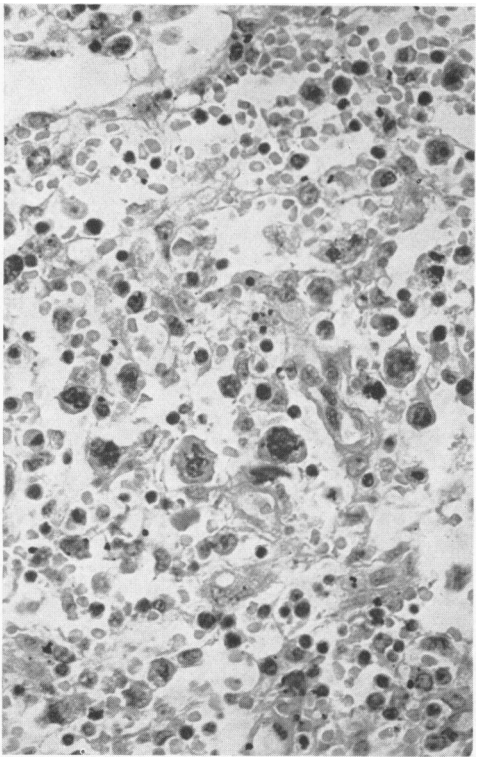

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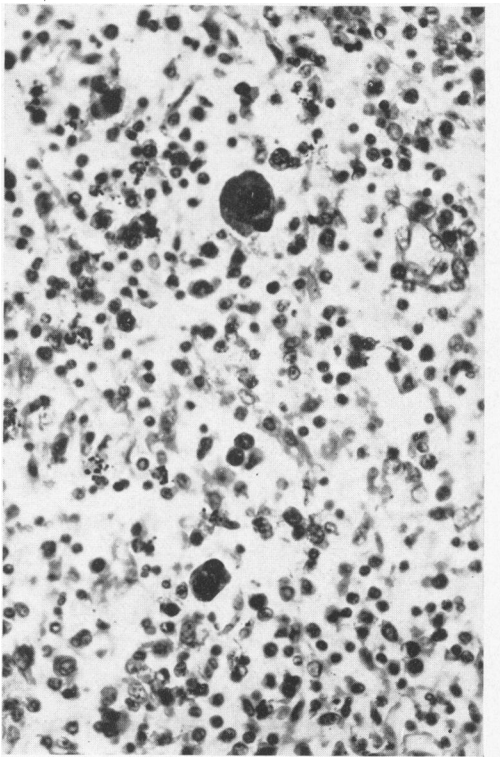

54

PLATE 138

FIG. 55. Group II. Bone marrow, rib. Extreme hypoplasia, "type A" marrow. K-119. Nagado. Female, 26 years of age. Approximately 1300 yds. Died on the 23rd day. A.I.P. neg. HM 340. × 13.

FIG. 56. Group II. Bone marrow, rib. Hypoplasia, "type A" marrow. Reticulum cells and plasmacytoid elements. Giemsa's stain. K-39. Takeuchi. Male, 29 years of age. Approximately 1000 yds. Died on the 29th day. A.I.P. neg. HM 184. × 180.

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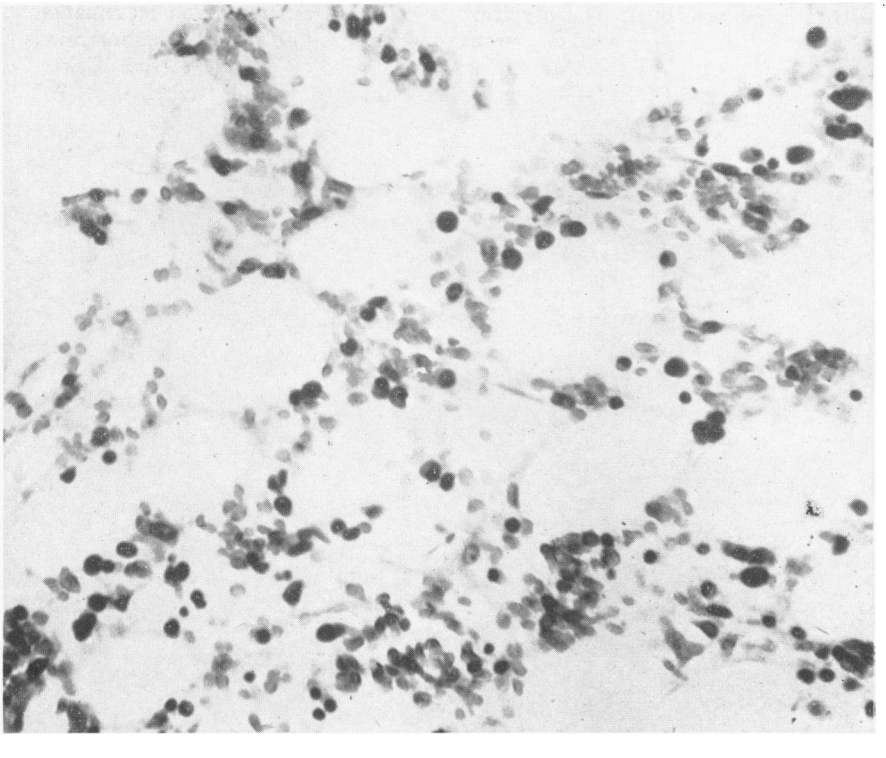

PLATE 139

FIG. 57. Group III. Rib. Costochondral junction. Hyperplasia of bone marrow, "type C" marrow. K-133. Nagai. Male, 9 years of age. Approximately 500 yds. Died on the 54th day. A.I.P. neg. HM 337. × 13.

FIG. 58. Group I. Bone marrow, sternum. Hypoplasia. Plasma cells arranged adventitially in relation to the sinusoids. Some large cells intermediate in appearance between the plasma cells and elements of the reticulum. This is the earliest histologic specimen of marrow available from a bone in which there is usually active hemopoiesis. Its classification is "type A," marked hypoplasia. K-98. Tamai. Male, 19 years of age. Distance unknown. Died on the tenth day. A.I.P. neg. HM 283. × 400.

FIG. 59. Group I. Bone marrow. Many plasma cells. Focal hyperplasia of reticulum. Some cells intermediate in appearance between plasma cells and elements of the reticulum. The atypical plasmacytoid differentiation is remarkable. No erythropoietic tissue or megakaryocytes are in evidence. This marrow is classified as "type B," marked focal reticulum hyperplasia. K-100. Ueki. Female, 32 years of age. Distance unknown. Died on the twelfth day. A.I.P. neg. HM 284. × 400.

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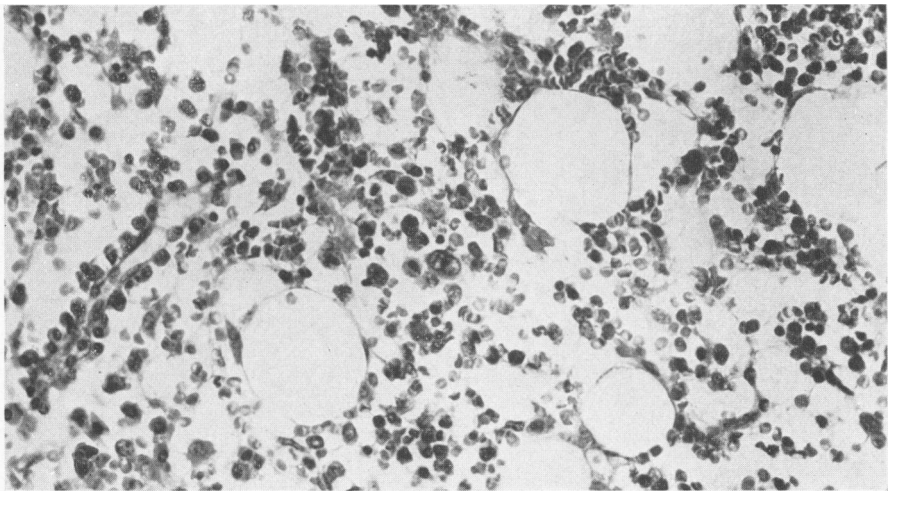

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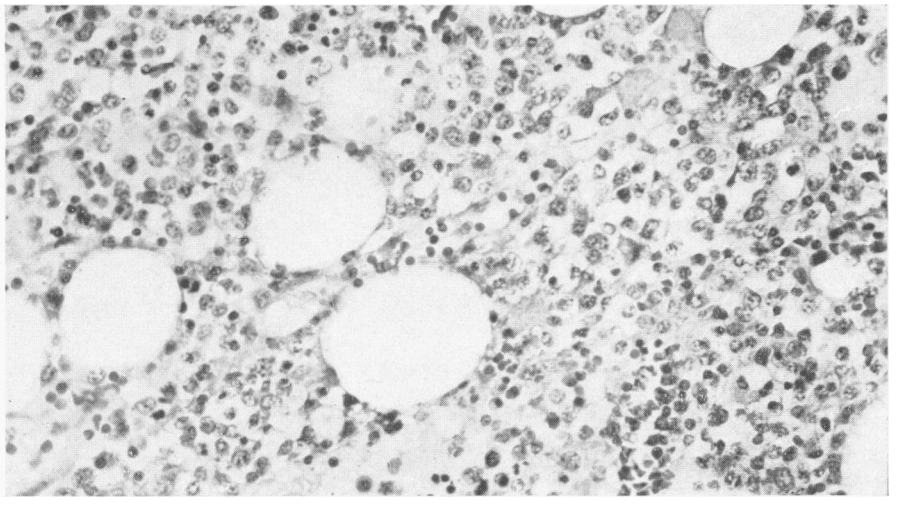


PLATE 140

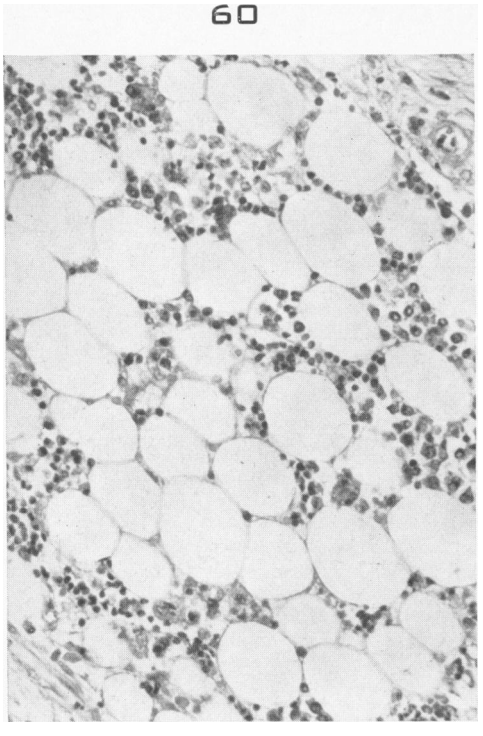
FIG. 60. Group II. Bone marrow (femoral). General view. Groups of reticulum cells, lymphocytes, and plasmacytoid elements. Islets of erythropoietic tissue persist. "Type A" marrow. K-25. Shintaku. Male, age unknown. Approximately 1000 yds. Died on the 25th day. A.I.P. neg. HM 195. × 230.

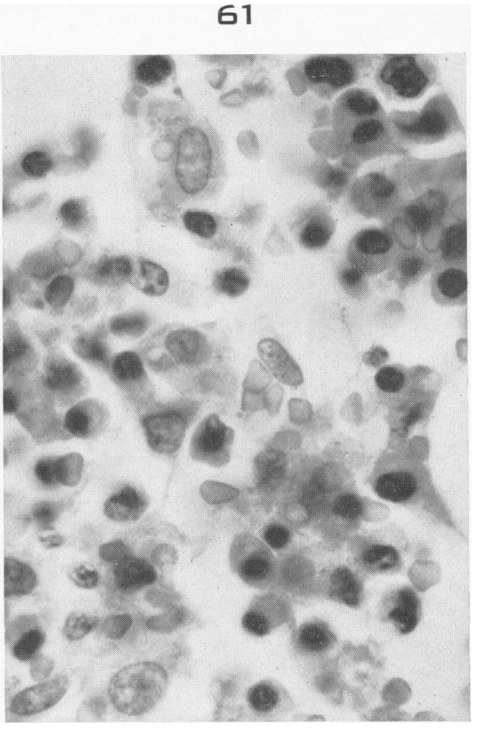
FIG. 61. Group II. Bone marrow. Femoral. "Type A" marrow. Reticulum and plasma cells. Erythrophagocytosis. K-28. Kawaura. Male, 23 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 200. × 1000.

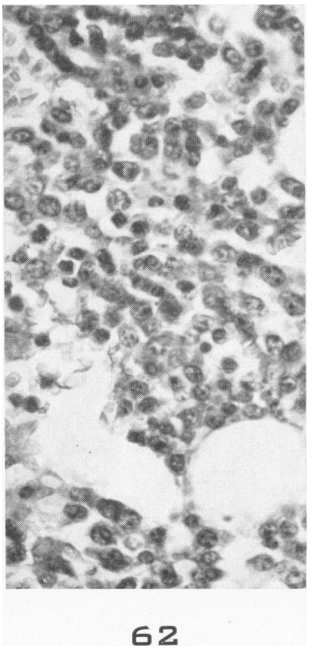
FIG. 62. Group II. Vertebral marrow. Hyperplasia of reticulum cells. "Type B" marrow. K-22. Michihara. Male, 17 or 23 years of age (variously stated). Approximately 1000 yds. Died on the 25th day. A.I.P. neg. HM 147. × 450.

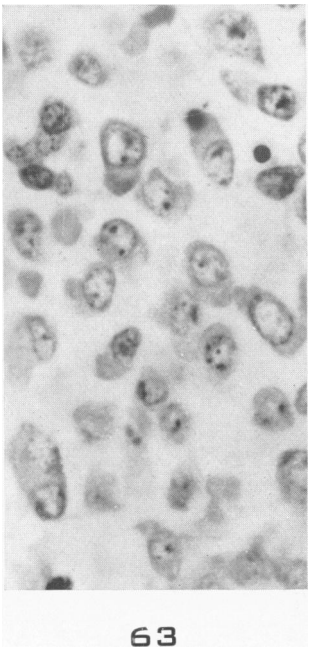
FIG. 63. Group II. Bone marrow. Reticulum cell hyperplasia. "Type B" marrow. Prominent nucleoli in some cells. Some cells are still spindle-shaped and others have become rounded. Some plasma cells are present. Giemsa's stain. K-41. Takano. Male, 23 years of age. Approximately 1000 yds. Died on the 30th day. A.I.P. neg. HM 324. × 1020.

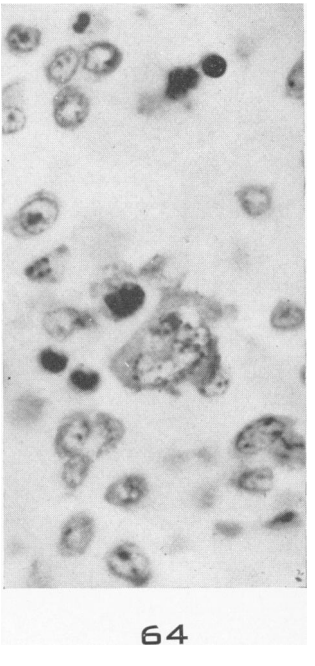
FIG. 64. Group II. Reticulum hyperplasia. Giant cell, possibly immature megakaryocyte. From the same patient as Figure 63. A.I.P. neg. HM 323. × 1020.




Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

## PLATE 141

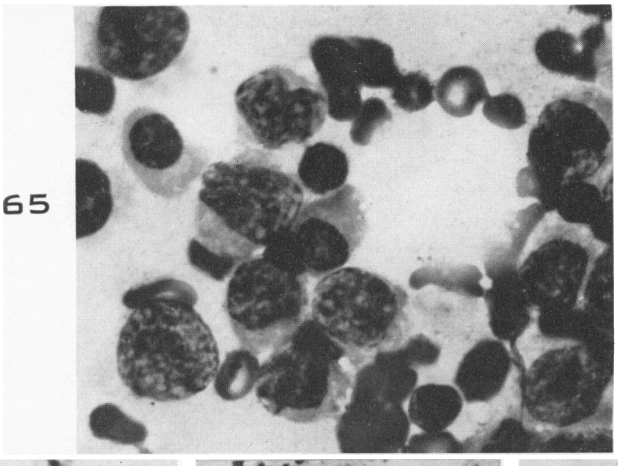
FIG. 65. Group II. Bone marrow, sternum. Reticulum cells, young myelocytes, and plasma cells. K-27. Omura. Male, 22 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 250. × 1000.

FIG. 66. Group II. Bone marrow, vertebral. Streptococci in wall of sinusoid, without local tissue response. Numerous large reticulum cells. Giemsa's stain. K-22. Michihara. Male, 23 or 17 years of age (variously stated). Died on the 25th day. A.I.P. neg. HM 183. × 1100.

FIG. 67. Group II. Bone marrow, rib. Focus of necrosis. Masses of bacteria. Giemsa's stain. K-39. Takeuchi. Male, 29 years of age. Approximately 1000 yds. Died on the 29th day. A.I.P. neg. HM 197. × 230.

FIG. 68. Group II. Bone marrow, rib. Bacilli in large numbers, without cellular reaction. Giemsa's stain. Enlargement of a portion of Figure 67. A.I.P. neg. HM 198. × 1000.

FIG. 69. Group III. Hyperplasia of reticulum. Some cells have more prominent nucleoli than are seen in the typical reticulum cell and may be forms in transition to myelocytes, although the granules in the cytoplasm are not seen. Blast cells are rare. K-118. Inaba. Female, 56 years of age. Approximately 700 yds. Died on the 60th day. A.I.P. neg. HM 316. × 750.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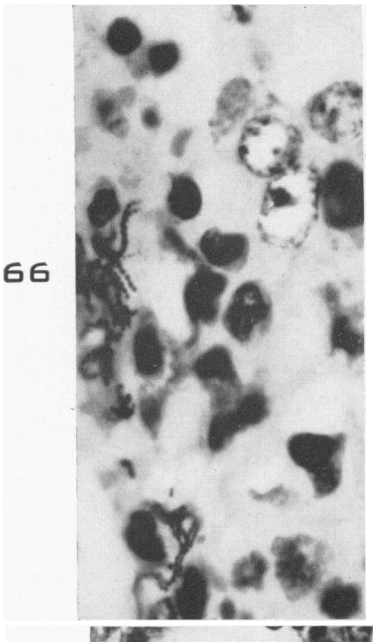
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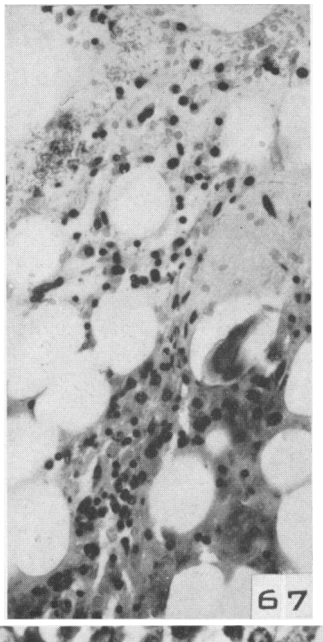
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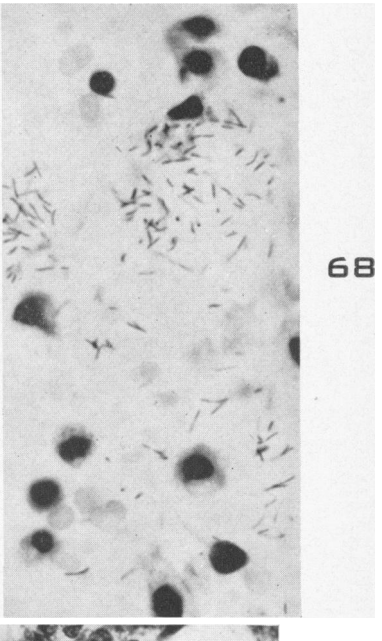
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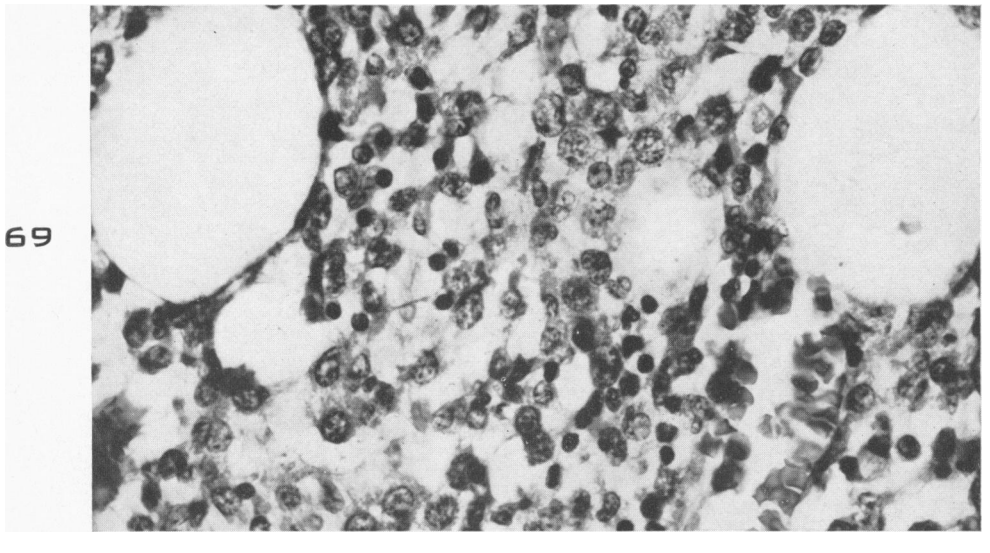

69

PLATE 142

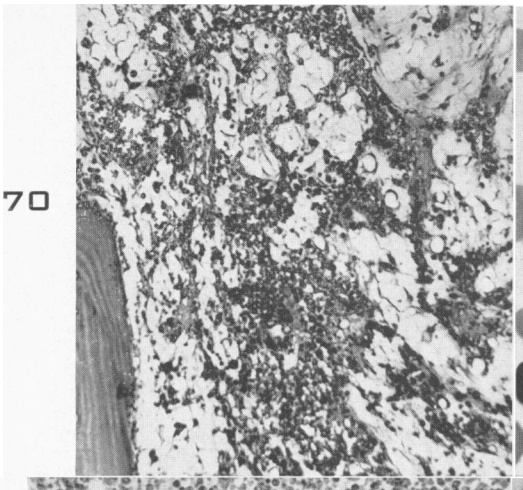
FIG. 70. Group III. Bone marrow of rib. Focus of regenerating tissue within the gelatinous marrow. "Type C" marrow. The vertebral marrow in this patient was much more cellular. K-50. Kijima. Male, 31 years of age. Approximately 1000 yds. Died on the 100th day. A.I.P. neg. HM 142a. × 115.

FIG. 71. Group III. Bone marrow smear. Myelocytes and a cell with clear cytoplasm resembling that of a lymphocyte. From the same patient as Figure 70. A.I.P. neg. HM 309. × 800.

FIG. 72. Group III. Bone marrow. Extreme hyperplasia, "Type D" marrow. Myelocytes and metamyelocytes predominate. Small islands of erythropoietic tissue. K-14. Yamamoto. Male, 25 years of age. Approximately 1000 yds. Died on the 47th day. A.I.P. neg. HM 261. × 130.

FIG. 73. Group III. Bone marrow, sternal. Fibrin deposited about megakaryocytes. K-110. Watanabe. Male, 56 years of age. Approximately 1000 yds. Died on the 27th day. A.I.P. neg. HM 287. × 500.

FIG. 74. Group III. Bone marrow, rib. "Gelatinous marrow" showing atrophic fat cells, and granular interstitial material containing large quantities of fibrin. Masson's stain. K-50. Kijima. Male, 31 years of age. Approximately 1000 yds. Died on the 100th day. A.I.P. neg. HM 266. × 400.



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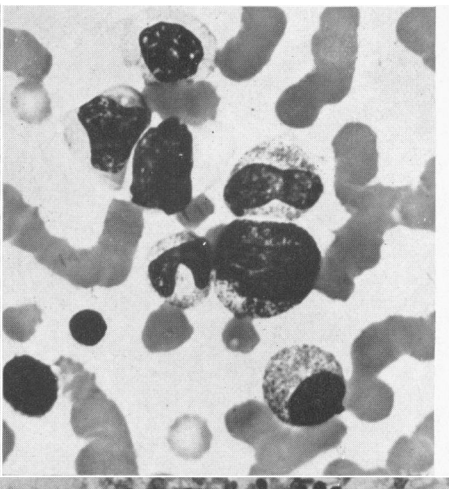

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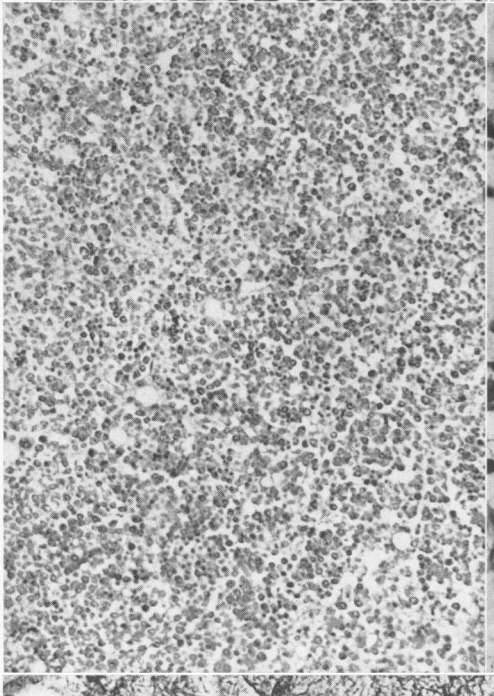

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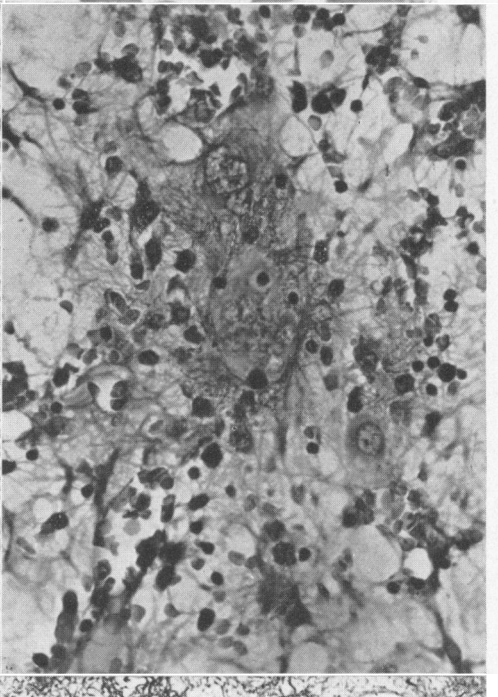

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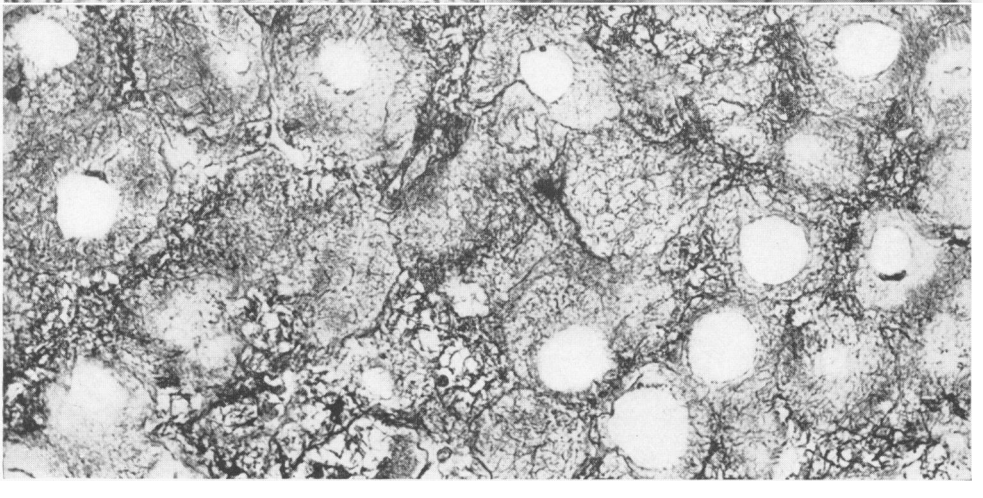

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PLATE 143

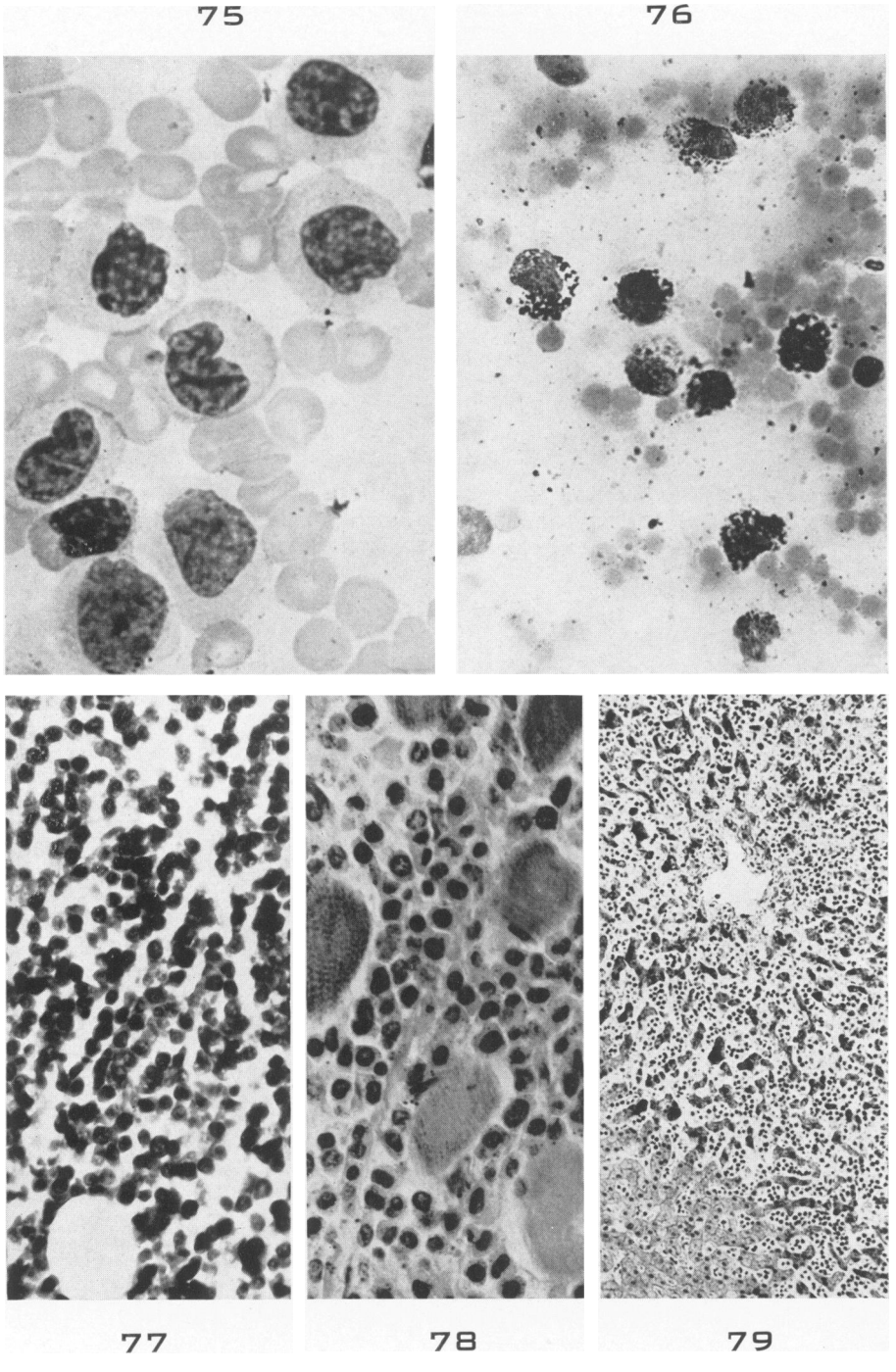
FIG. 75. Group III. Peripheral blood film. Cells of monocytic type. K-224. (Nagasaki.) Matsuo. Male, 19 years of age. Approximately 1000 yds. Died on the 97th day. A.I.P. neg. NM 163. × 1100.

FIG. 76. Group III. Supravital blood film of November 16, 1945, showing phagocytosis of carbon by the atypical mononuclear cells. From the same patient as Figure 75. A.I.P. neg NM 158. Copy of Japanese photograph.

FIG. 77. Group III. Bone marrow (probably from long bone). Large mononuclear cells forming thick septa among the fat cells. From the same patient as Figure 75. A.I.P. neg. NM 164. × 400.

FIG. 78. Group III. Striated muscle. Atypical large mononuclear cells infiltrating among the fibers. Phosphotungstic acid-hematoxylin stain. From the same patient as Figure 75. × 500.

FIG. 79. Group III. Liver. Pericentral infiltration of large mononuclear elements. Atrophy of central ends of hepatic cell cords. From the same patient as Figure 75. A.I.P. neg. NM 162. × 120.

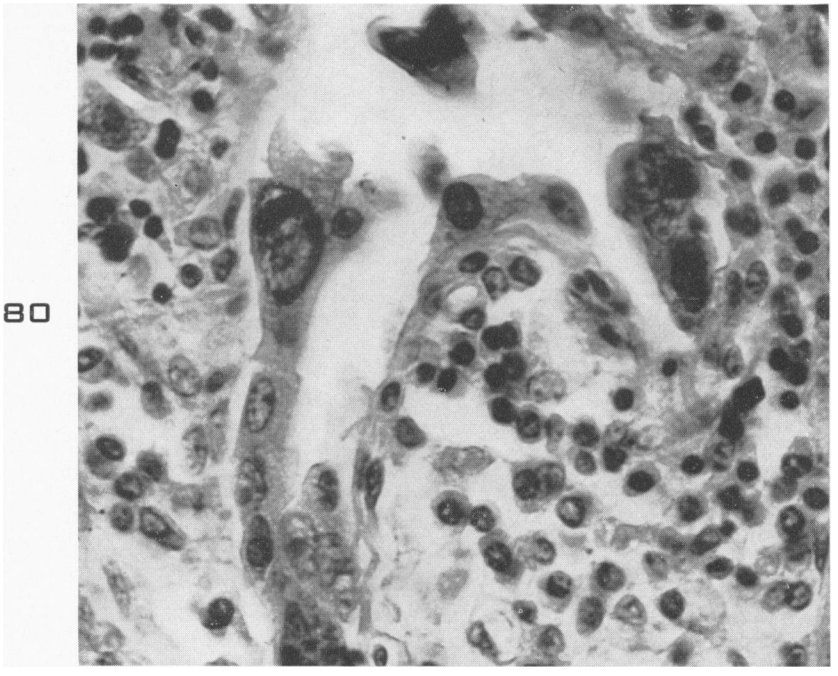



Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 144

FIG. 80. Group I. Ileum. Epithelial cell with enormous nucleus at base of crypt. Abundant plasmacytoid cells in the lamina propria. K-5. Yano. Male, 39 years of age. Approximately 1000 yds. Died on the sixth day. A.I.P. neg. HM 127. × 810.

FIG. 81. Group I. Intestine. Base of crypt. Slightly below and to the left of the center there is an epithelial cell in tripolar mitosis. K-2. Onishi. Male, 24 years of age. Approximately 800 yds. Died on the fourth day. A.I.P. neg. HM 125. × 650.



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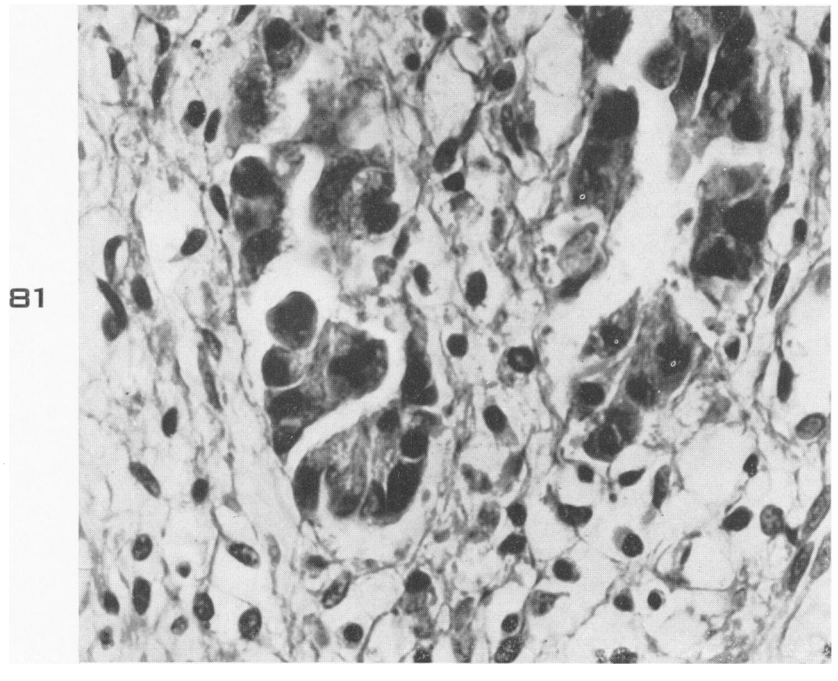

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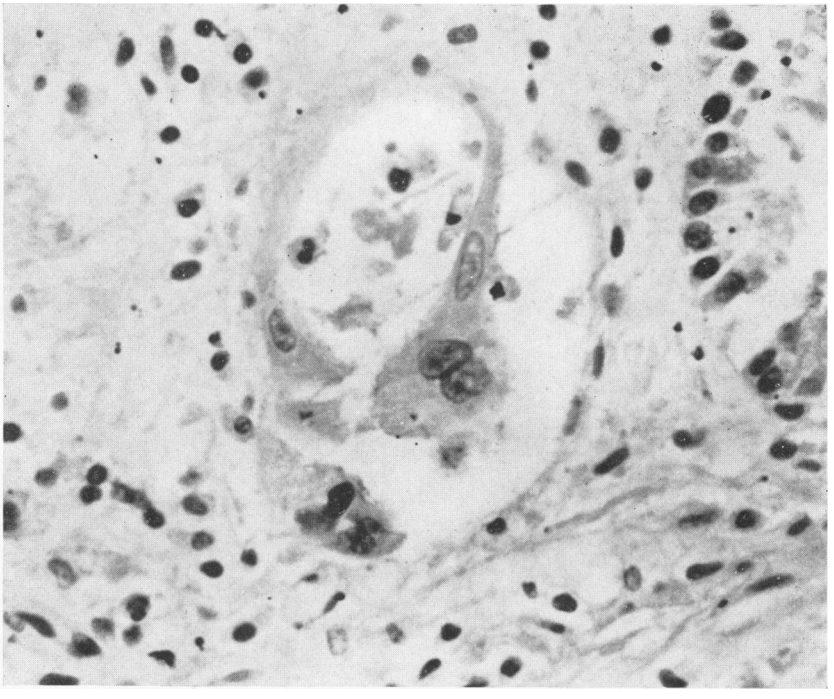
PLATE 145

FIG. 82. Group I. Intestine. Atypical epithelial cells at base of crypt. K-175. (Nagasaki.) Yamada. Female, 18 years of age. Distance unknown. Died on the eleventh day. A.I.P. neg. NM 159. × 600.

FIG. 83. Group I. Intestine. Superficial ulcers containing masses of bacteria. Edema of submucosa. No leukocytic infiltration. From the same patient as Figure 82. × 25.

82



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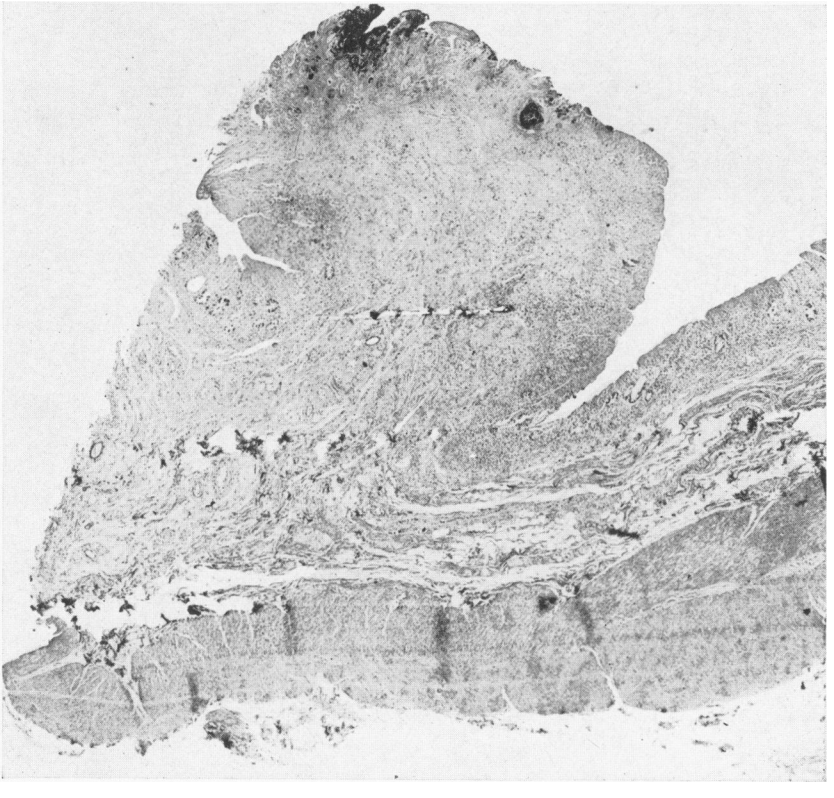
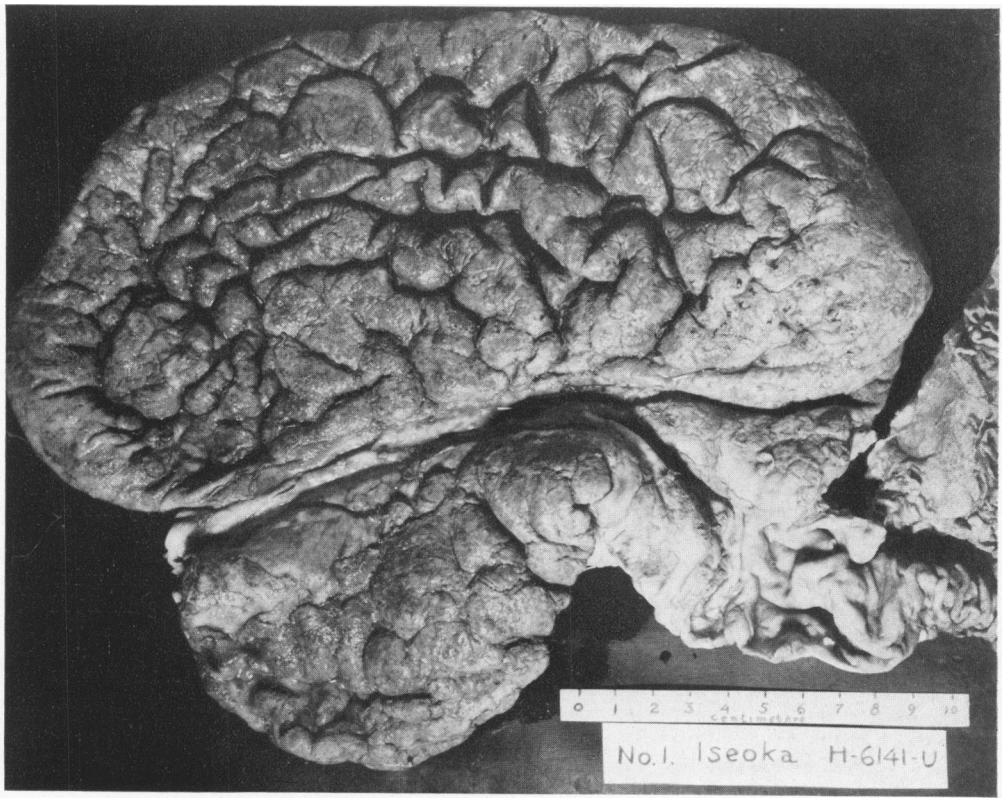


PLATE 146

FIG. 84. Group II. Stomach. Edema, hemorrhage, necrosis, and superficial ulcers of mucosa of stomach. The process is diffuse, except for a narrow band of well preserved mucous membrane along the lesser curvature and in a few places elsewhere. K-21. Iseoka. Male, 45 years of age. Approximately 1000 yds. Died on the 24th day. A.I.P. neg. HS 301.

FIG. 85. Group II. Ileocecal valve. Necrosis and hemorrhage of ileocecal valve and ascending colon. K-37. Takeda. Male, 25 years of age. Approximately 1000 yds. Died on the 29th day. A.I.P. neg. HS 320.

84

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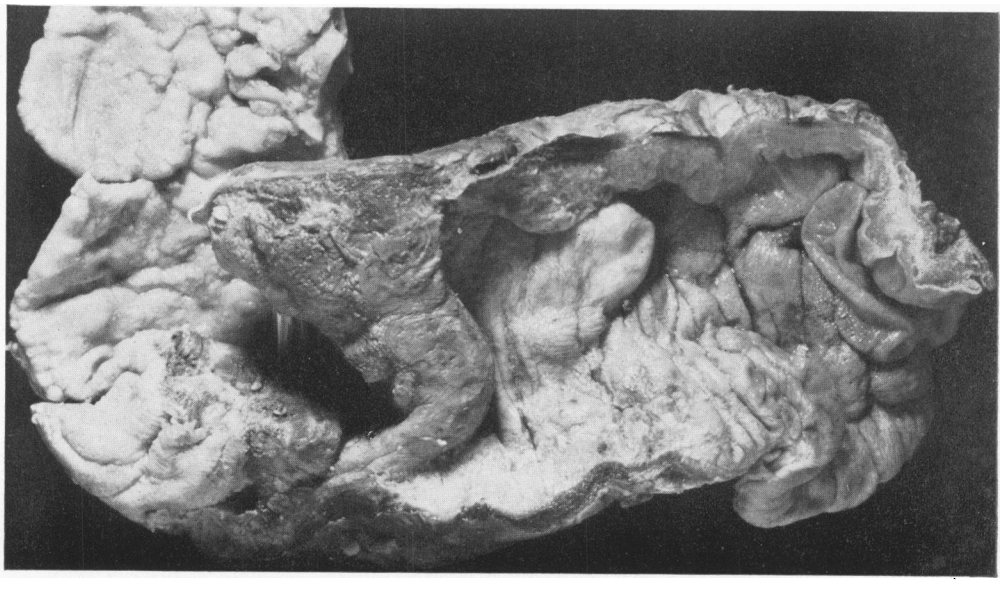


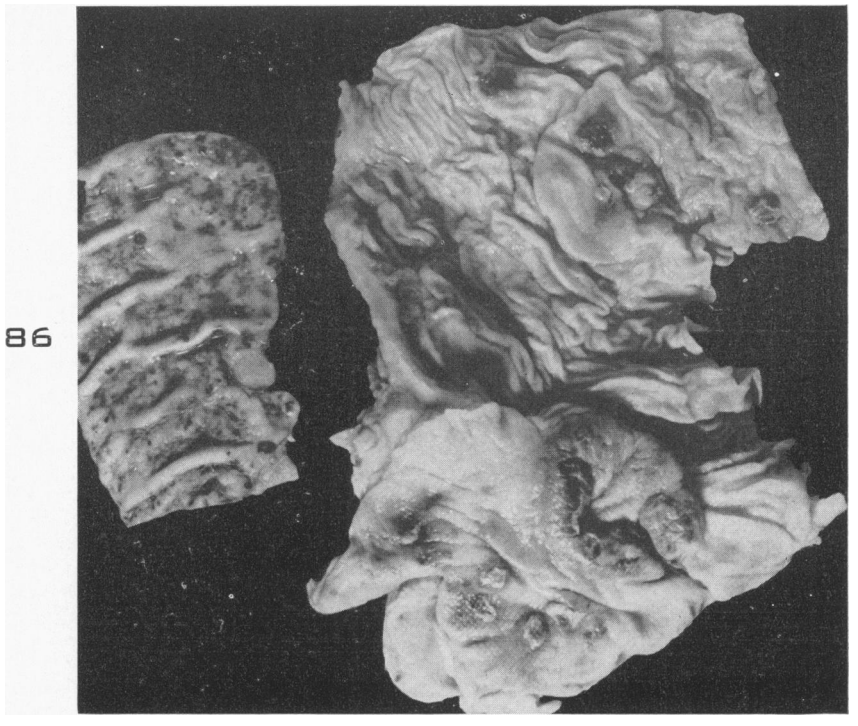
Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 147

FIG. 86. Group II. Intestine. Focal hemorrhages of ileum. Hemorrhages and ulcers of ascending colon and ileocecal valve. K-35, Takahashi. Male, 31 years of age. Approximately 1000 yds. Died on the 28th day. A.I.P. neg. HS 317.

FIG. 87. Intestine. Necrosis and hemorrhage of mucous membrane. Ileocecal valve involved. K-27. Omura. Male, 22 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HS 306.

FIG. 88. Group II. Large intestine. Ulceration of mucous membrane. Fibrinous exudate adheres in large, irregular shreds. Diffuse hemorrhage of submucosa. K-38. Kamihara. Male, 22 years of age. Approximately 1000 yds. Died on the 29th day. A.I.P. neg. HS 321.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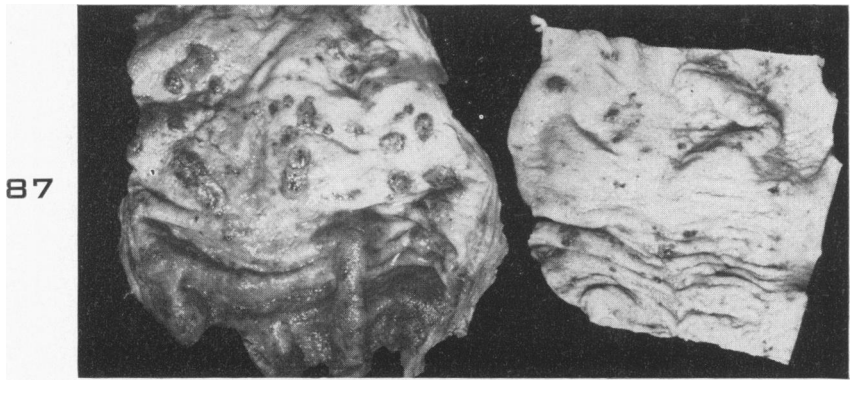
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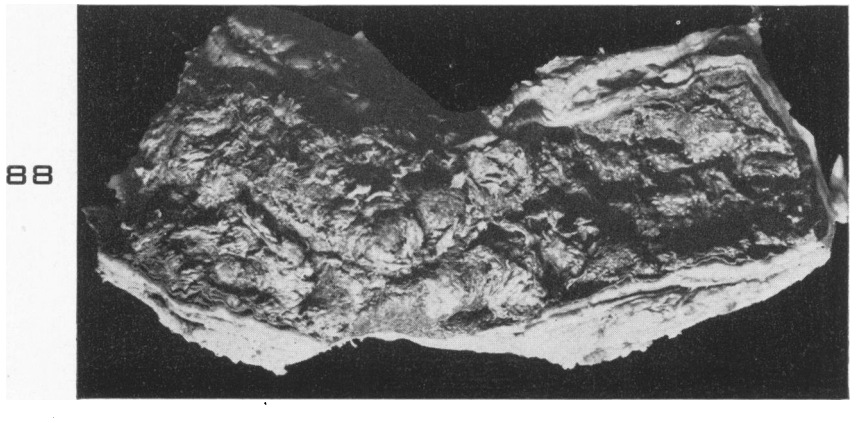

88

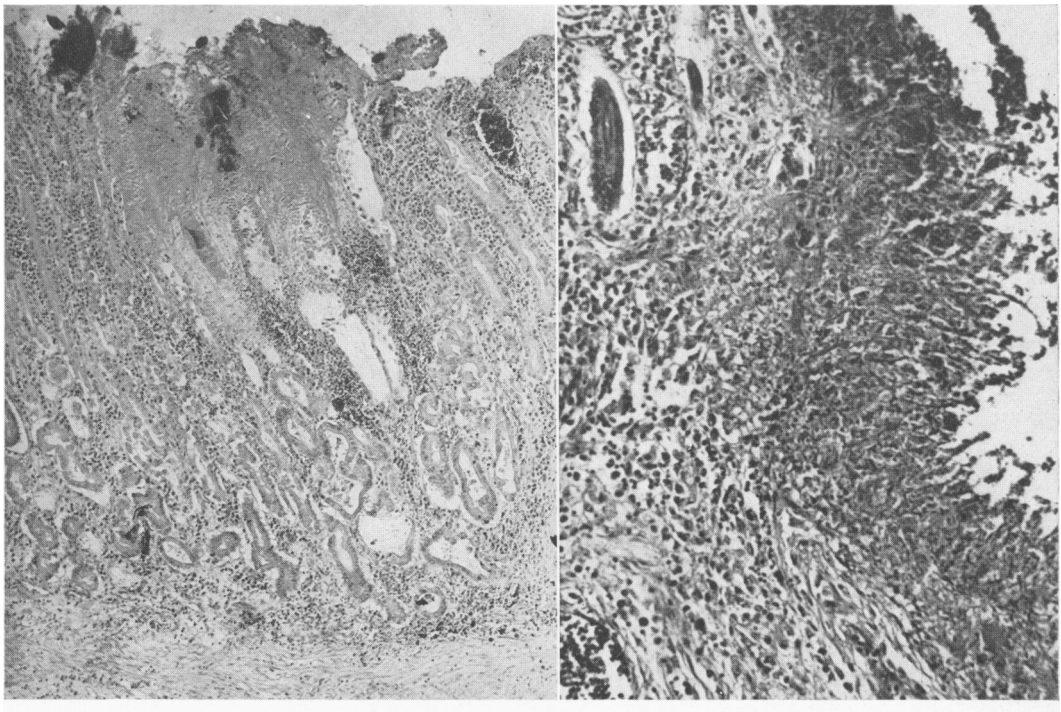
PLATE 148

FIG. 89. Group II. Stomach. Focal necrosis. Bacterial masses at surface. Plasma cell infiltration of wall. From the same patient as Figure 84. A.I.P. neg. HM 146. × 81.

FIG. 90. Group II. Margin of ulcer. The exudate consists of small and large mononuclear cells and plasma cells, without polymorphonuclear leukocytes. K-43. Horinouchi. Male, 33 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HM 235. × 130.

FIG. 91. Group II. Colon. Polypoid mass of necrotic tissue. Edema of mucosa and submucosa. No leukocytic infiltration.

FIG. 92. Group III. Colon. Amebae in edematous areolar tissue of the submucosa. K-131. Takatani. Female, 39 years of age. Approximately 1500 yds. Died on the 46th day. A.I.P. neg. HM 339. × 350.



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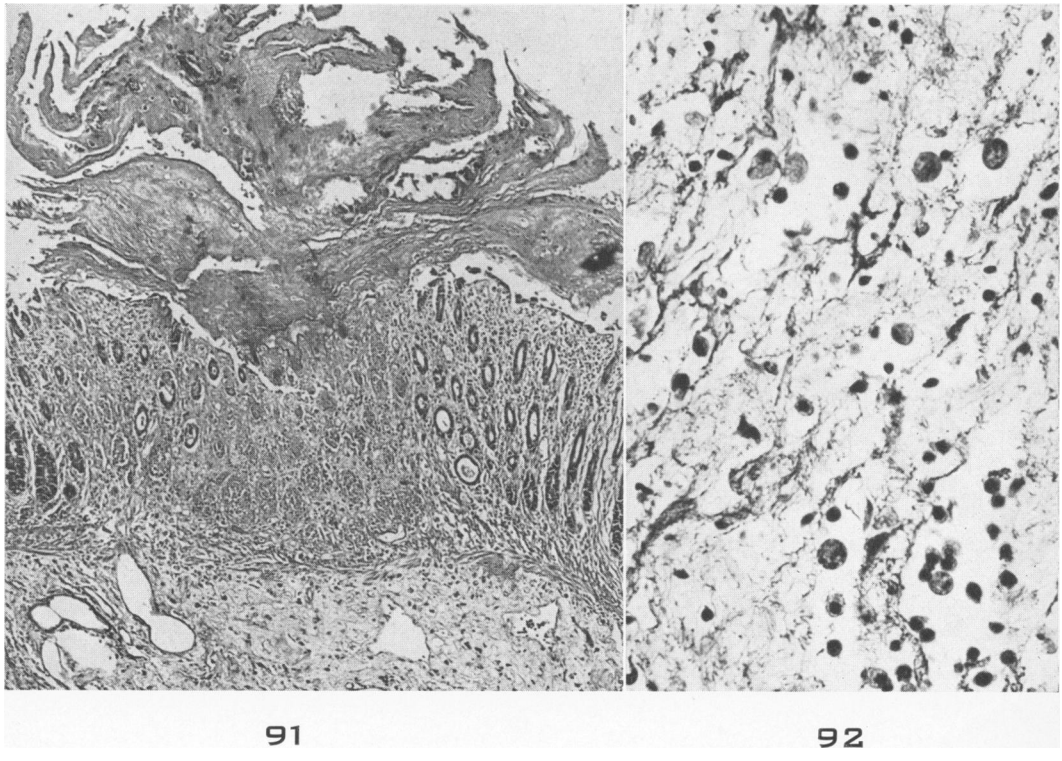


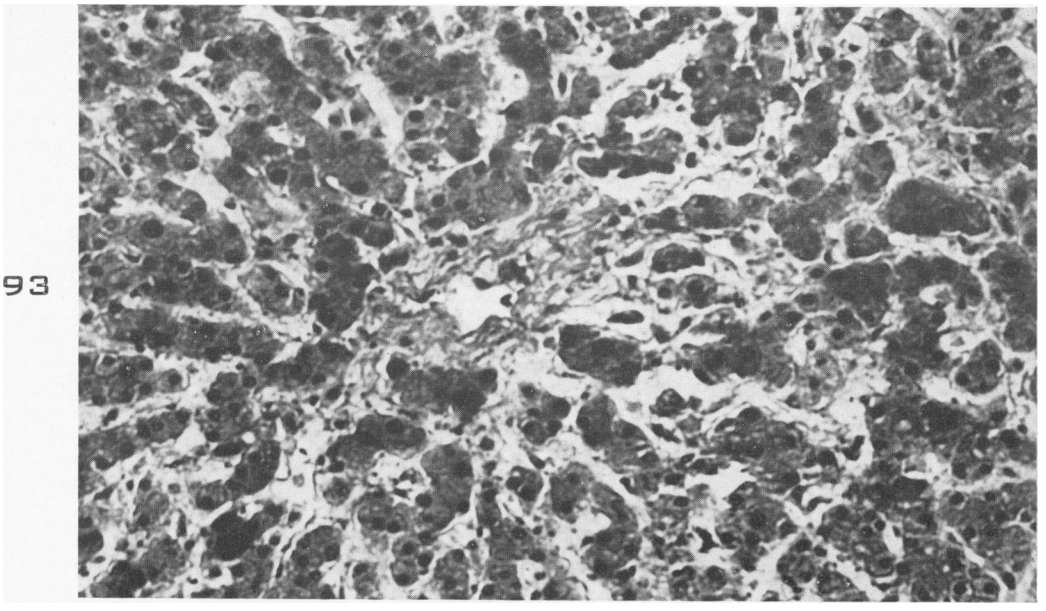
91 92

PLATE 149

FIG. 93. Group I. Liver. Central congestion. Edema of connective tissue about the central vein. Large nuclei in the cells of the cords nearest the central venules. K-2. Onishi. Male, 24 years of age. Approximately 800 yds. Died on the fourth day. × 250.

FIG. 94. Group II. Liver. Focus of necrosis. The cellular exudate is scanty and consists almost entirely of plasma cells, many of which are represented only by granular pyknotic débris. K-89. Kuroki. Male, 23 years of age. Approximately 1000 yds. Died on the 21st day. A.I.P. neg. HM 273. × 200.

FIG. 95. Group III. Liver. Central necrosis; thickening of wall of central venule. Exudate of small and large mononuclear cells. K-14. Yamamoto. Male, 25 years of age. Approximately 1000 yds. Died on the 47th day. A.I.P. neg. HM 212. × 115.



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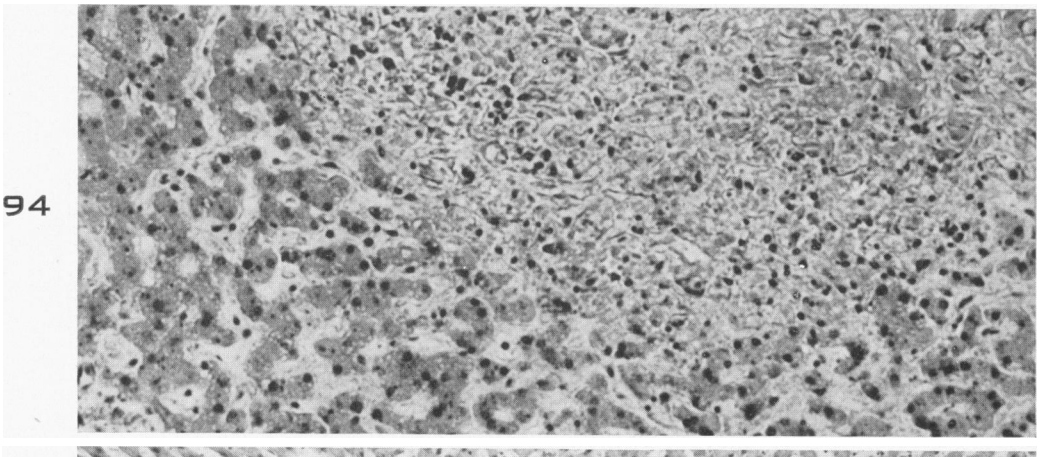

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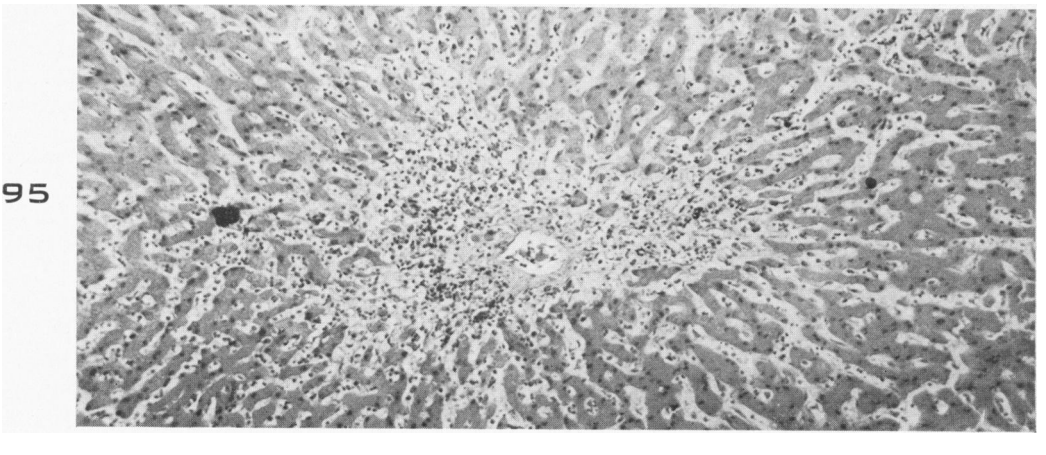


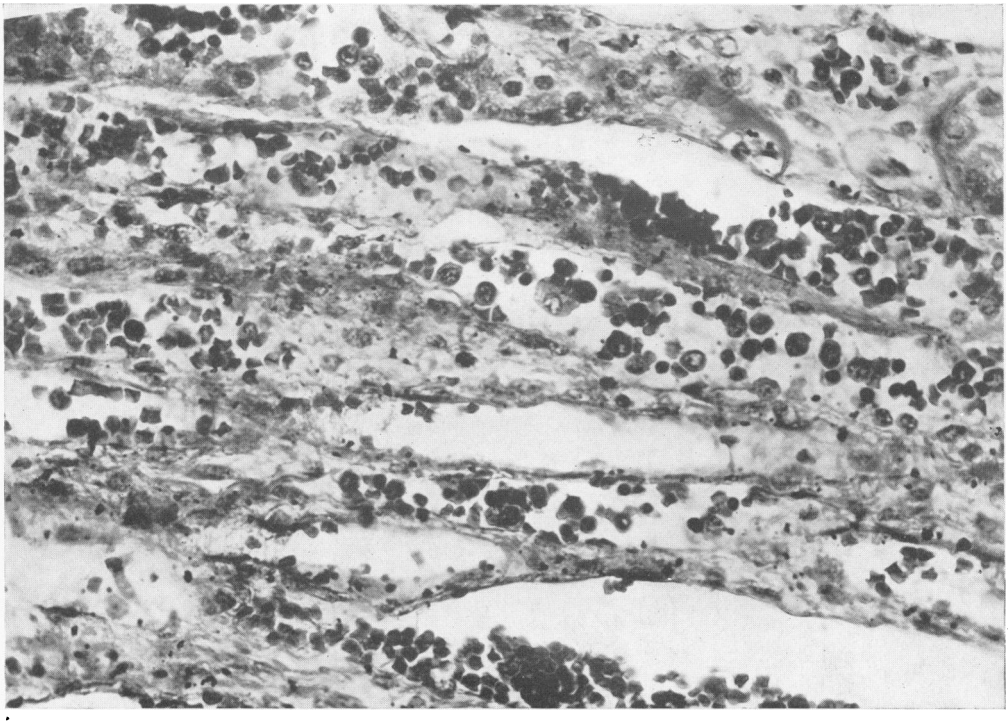
95

PLATE 150

FIG. 96. Group I. Kidney. Sinusoids at corticomedullary junction containing large mononuclear cells, one in mitosis. K-9. Sakamoto. Male, 25 years of age. Approximately 1500 yds. Died on the eighth day. A.I.P. neg. HM 137. × 400.

FIG. 97. Group II. Kidney. Petechiae in parenchyma of kidney, hemorrhage in mucous membrane of pelvis. There was no evidence of glomerulonephritis histologically. K-30. Nagashima. Male, 23 or 28 years of age (variously stated). Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HS 312.

96



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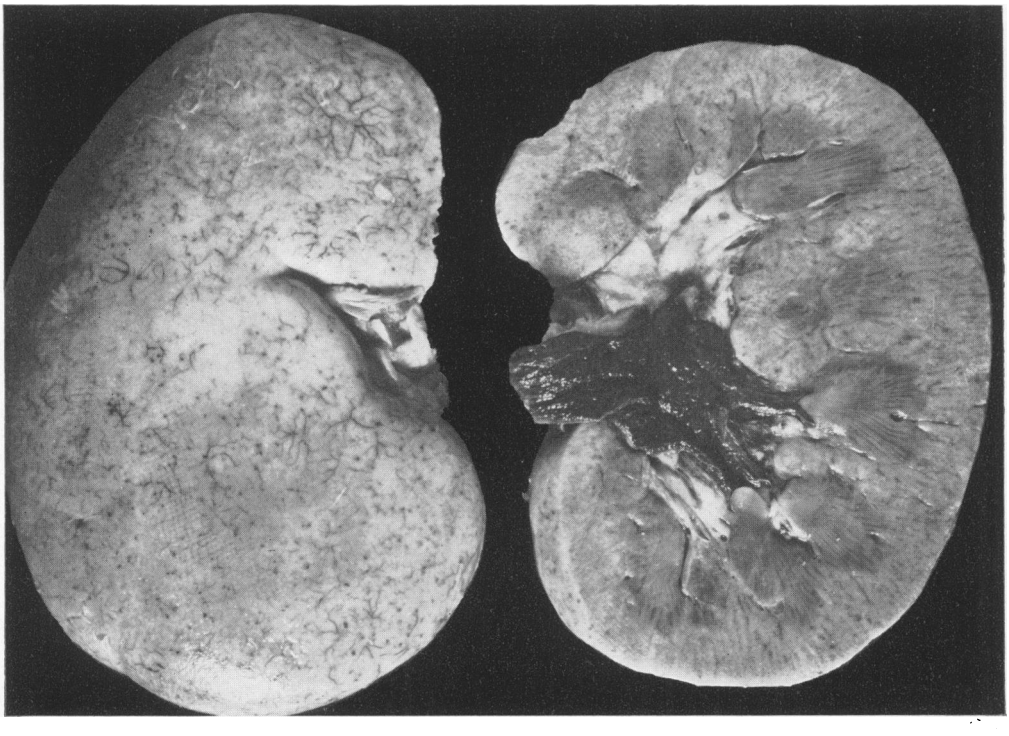


Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

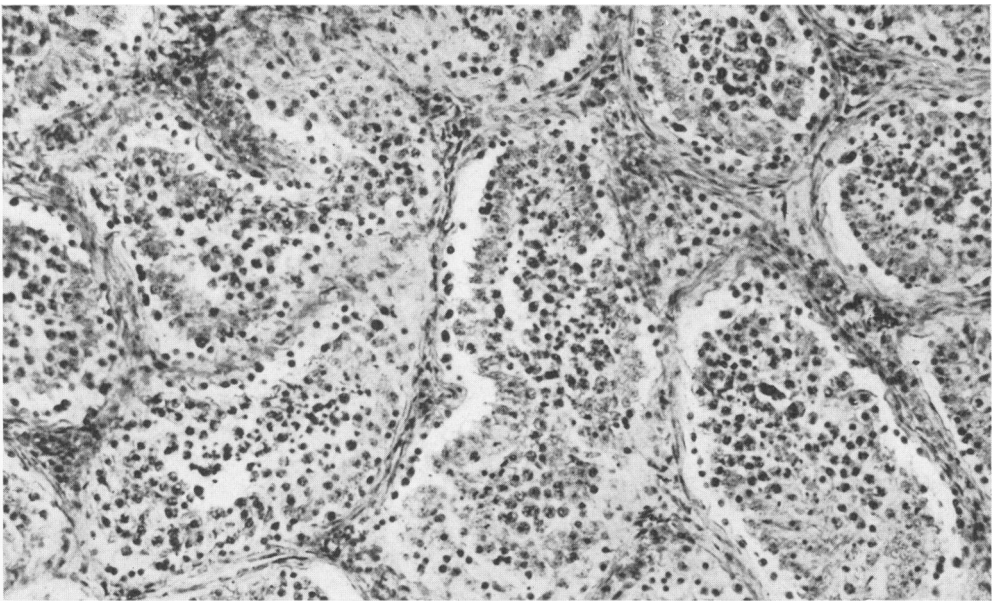
PLATE 151

FIG. 98. Group I. Testis. Sloughing of spermatogonia from basement membrane whereon rest Sertoli cells in increased numbers. Relatively few spermatids and mature spermatozoa in lumina of tubules. Mitotic figures are relatively rare. K-2. Onishi, 24 years of age. Approximately 800 yds. Died on the fourth day. A.I.P. neg. HM 122. × 160.

FIG. 99. Group II. Testes. Atrophy. K-30. Nagashima, 23 or 28 years of age (variously stated). Died on the 26th day. A.I.P. neg. HS 313.

FIG. 100. Group II. Testis. Atrophy. Necrotic remnants of germinal epithelium and its derivatives in lumina of tubules. Edema of interstitial tissues. Hyaline subendothelial changes of arterioles. K-28. Kawaura, 23 years of age. Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 150. × 125.

98



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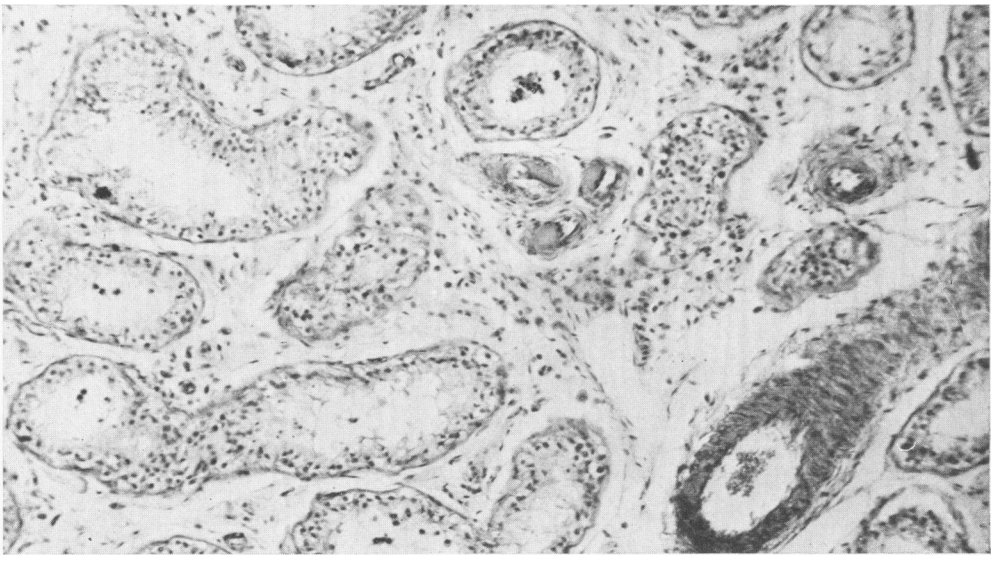


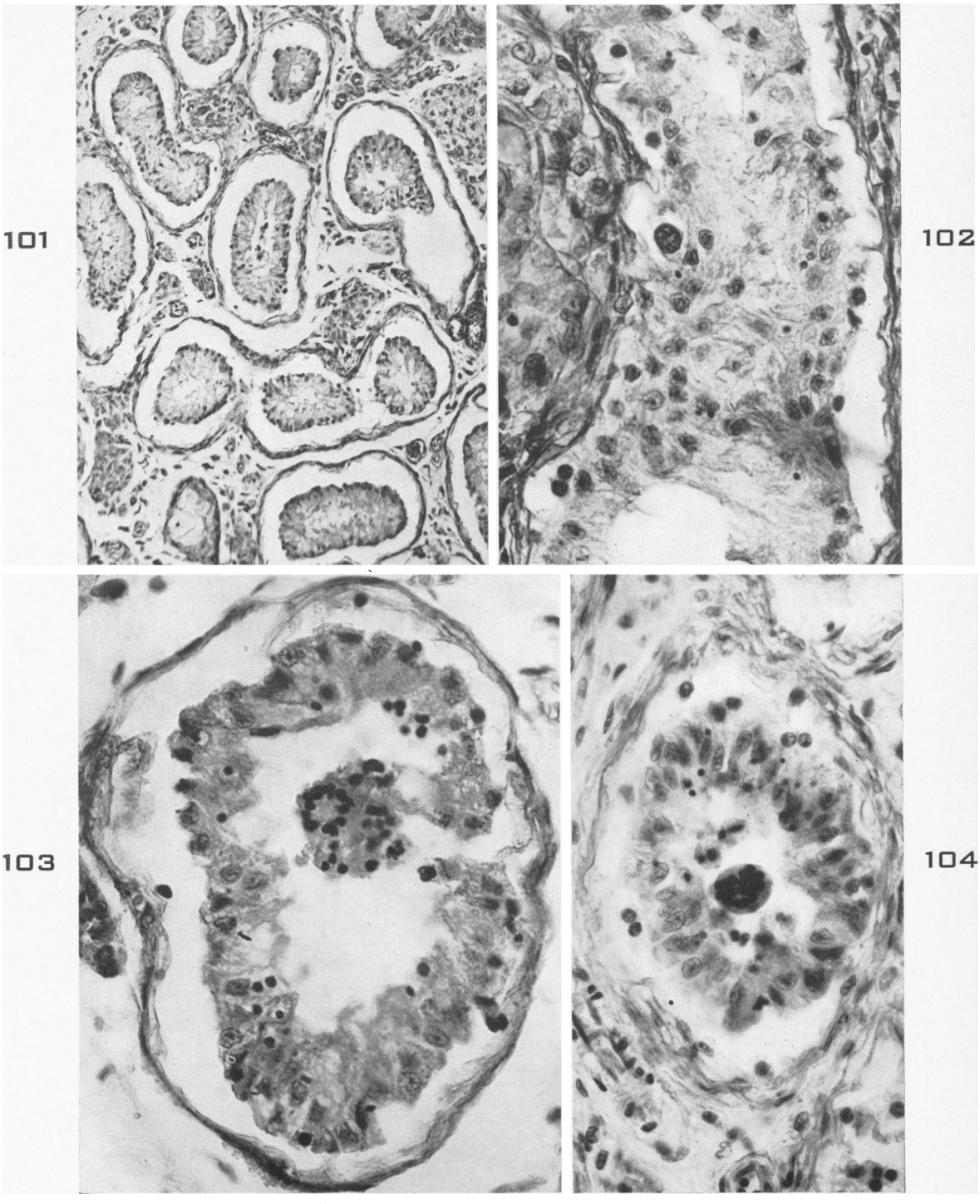
PLATE 152

FIG. 101. Group II. Testis. Atrophy of germinal epithelium and its derivatives. Hyperplasia of interstitial tissue. K-39. Takeuchi, 29 years of age. Approximately 1000 yds. Died on the 29th day. A.I.P. neg. HM 228. × 115.

FIG. 102. Group II. Testis. Atrophy of tubules. Near the basement membrane, among the Sertoli cells, is an ovoid cell with a hyperchromatic nucleus, considered to be a persistent element of the germinal epithelium. K-46. Kurihara, 22 years of age. Approximately 800 yds. Died on the 33rd day. A.I.P. neg. HM 241. × 450.

FIG. 103. Group II. Testis. Atrophy. Tubule containing "giant cell" apparently produced by fusion and compaction of the cytoplasm of spermatids, some of which are still isolated. K-40. Motoyama, 29 years of age. Approximately 1000 yds. Died on the 30th day. A.I.P. neg HM 231. × 450.

FIG. 104. Group II. Testis. Atrophy. "Giant cell" in lumen of tubule, which is lined by Sertoli cells. The "giant" cell probably has resulted from compaction and fusion of spermatids. K-91. Kato, 24 years of age. Approximately 1000 yds. Died on the 30th day. A.I.P. neg. HM 274. × 400.




Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

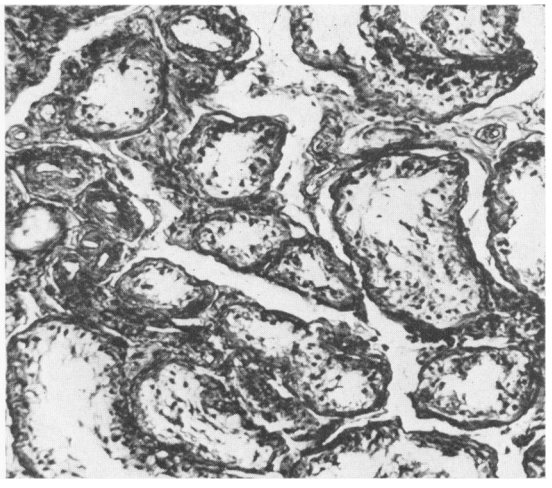
PLATE 153

FIG. 105. Group III. Testis. Cessation of spermatogenesis. The tubules, whose basement membranes have not become thickened, are lined exclusively by Sertoli cells. The interstitial tissue is not hyperplastic. K-50. Kijima, 31 years of age. Approximately 1000 yds. Died on the 100th day. A.I.P. neg. HM 143. × 115.

FIG. 106. Group III. Immature testis. Thickening of basement membranes of tubules. The epithelium appears slightly shrunken but otherwise well preserved. K-128. Fukuhara, 8 years of age. Between 500 and 1000 yds. Died on the 40th day. A.I.P. neg. HM 338. × 100.

FIG. 107. Group III. Prostate. Atrophy. Grossly, this prostate was approximately one-half the usual size. From the same patient as Figure 105. A.I.P. neg. HM 144. × 95.

105



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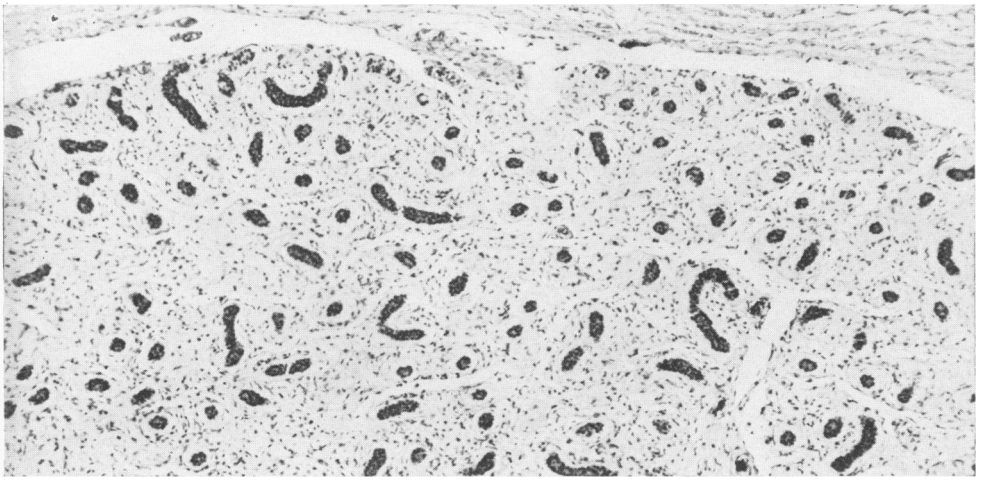

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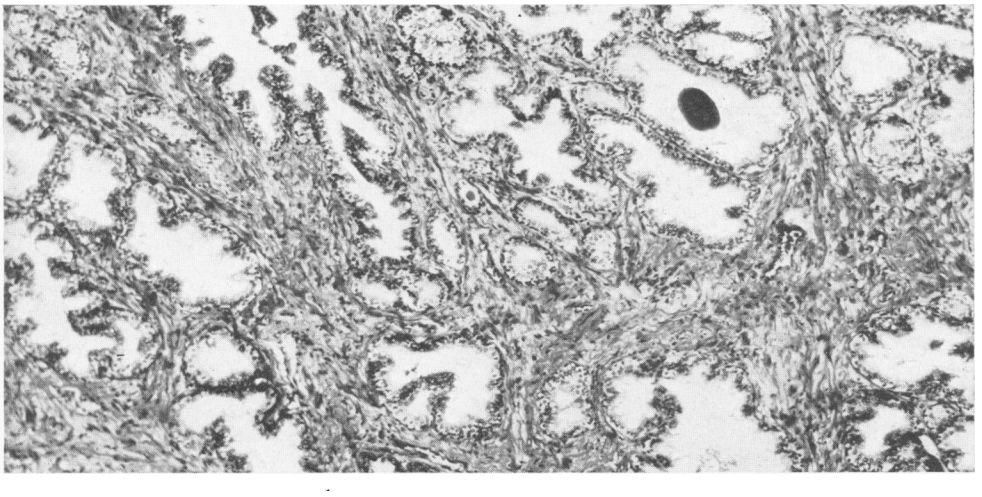


PLATE 154

FIG. 108. Group II. Pelvic organs. Hemorrhages in endometrium and in right ovary. K-36. Morita, 21 years of age. Approximately 1000 yds. Died on the 28th day. A.I.P. neg. HS 318.

FIG. 109. Group II. Ovary. Paucity of primary follicles. Atresia of surviving follicles. No developing follicles. Corpora albicantia present elsewhere in this ovary. K-119. Nagado, 26 years of age. Approximately 1300 yds. Died on the 23rd day. A.I.P. neg. HM 303. × 115.

108

109

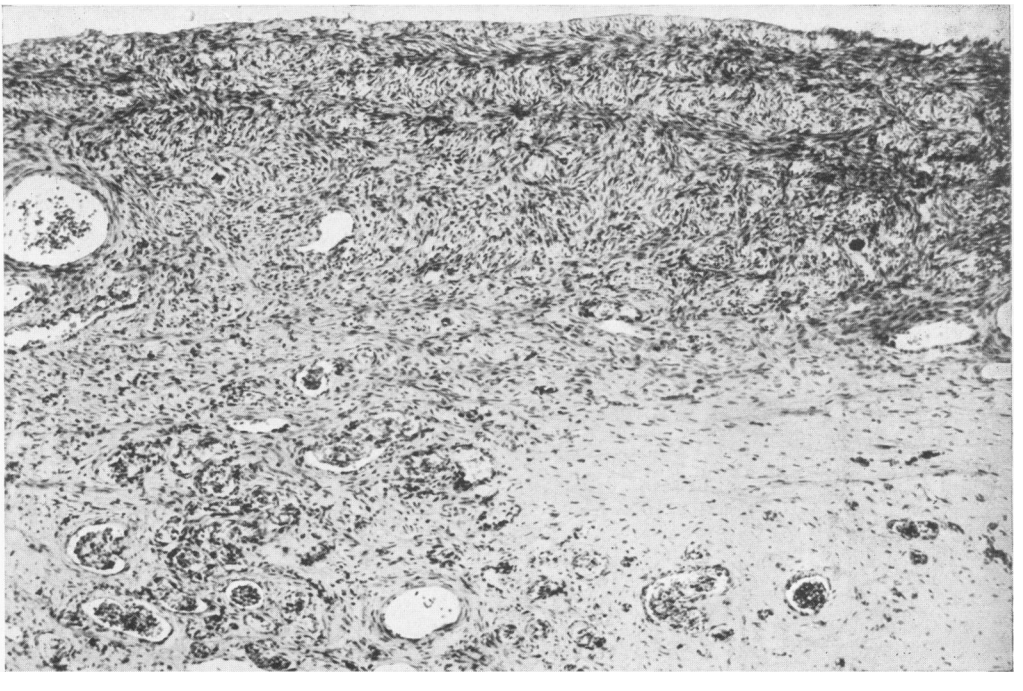


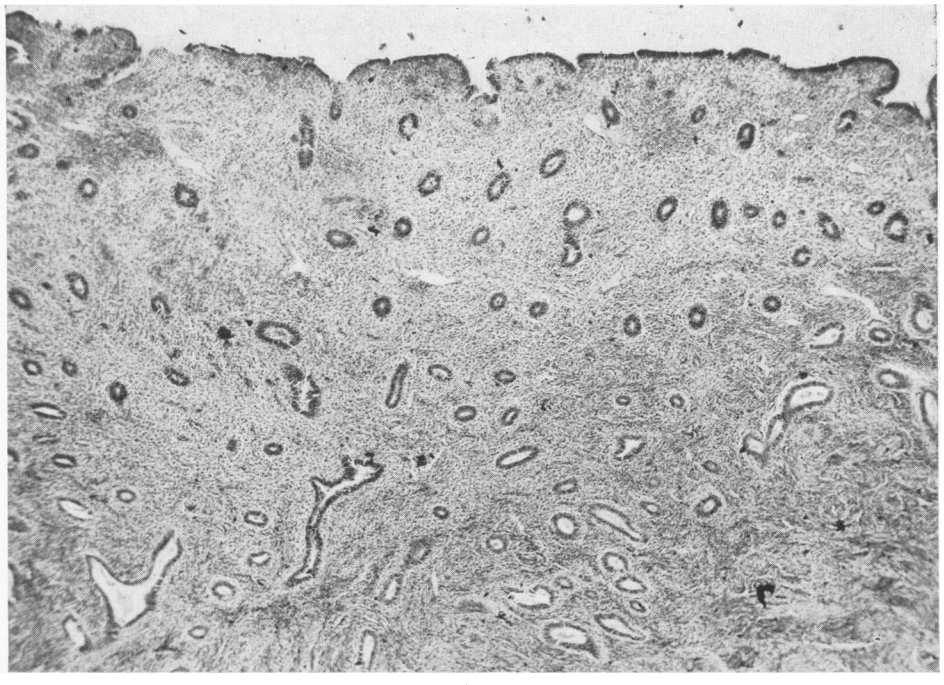
PLATE 155

FIG. 110. Group II. Endometrium in "resting phase." K-47. Naka, 35 years of age. Approximately 800 yds. Died on the 18th day. A.I.P. neg. HM 245. × 50.

FIG. 111. Group II. Ovary. Atretic follicle. Granulosa cells clumped at center. Enlargement of a portion of Figure 109. × 450.

FIG. 112. Group II. Ovary. Deposits of hyaline refractile acidophilic material beneath endothelium of blood vessels. Similar to changes seen in stroma of testis. From the same patient as Figure 109. A.I.P. neg. HM 30. × 175.

110



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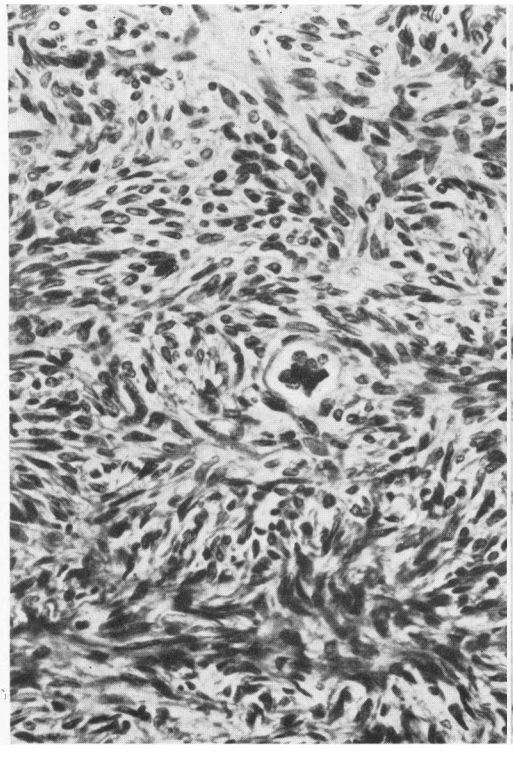


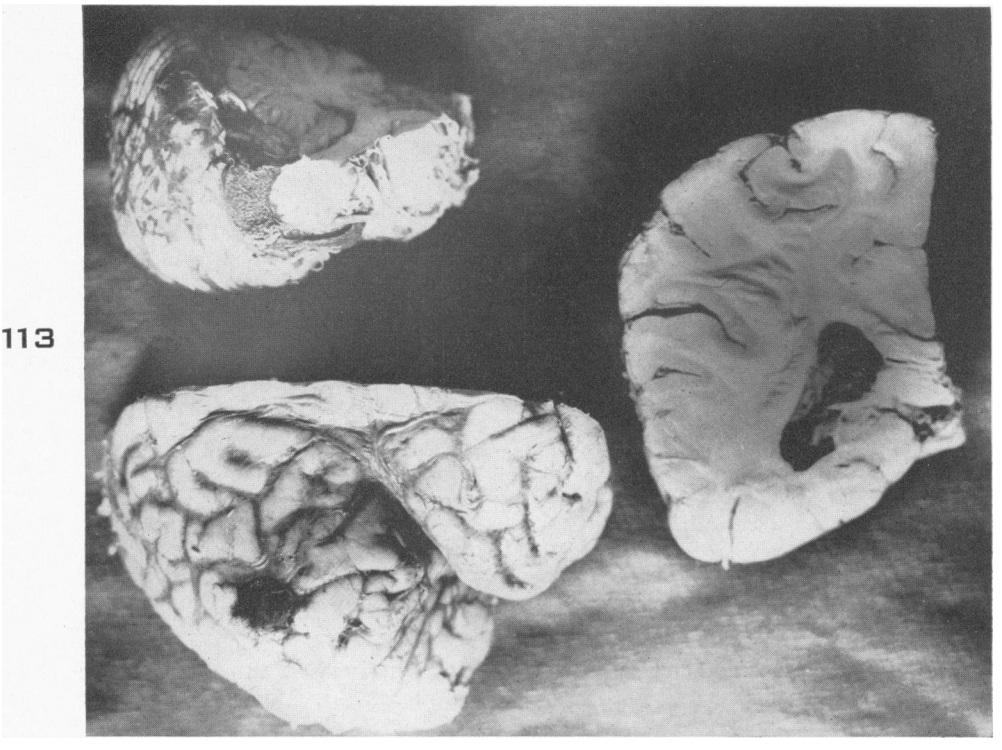
112

Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 156

FIG. 113. Group II. Sub-pial hemorrhage of frontal lobe. Massive hemorrhage in medullary cistern of sub-arachnoid space. Petechiae of sub-ependyma of lateral ventricle. K-42. Moriseko. Male, 27 years of age. Approximately 1000 yds. Died on the 31st day. A.I.P. neg. HS 324.

FIG. 114. Group II. Brain. Focus of necrosis in medulla, surrounded by hemorrhage. A small bacterial mass which appears black in the photomicrograph lies near the center of the lesion. K-60. Shigeta. Female, 44 years of age. Approximately 800 yds. Died on the 36th day. A.I.P. neg. HM 333. × 100.



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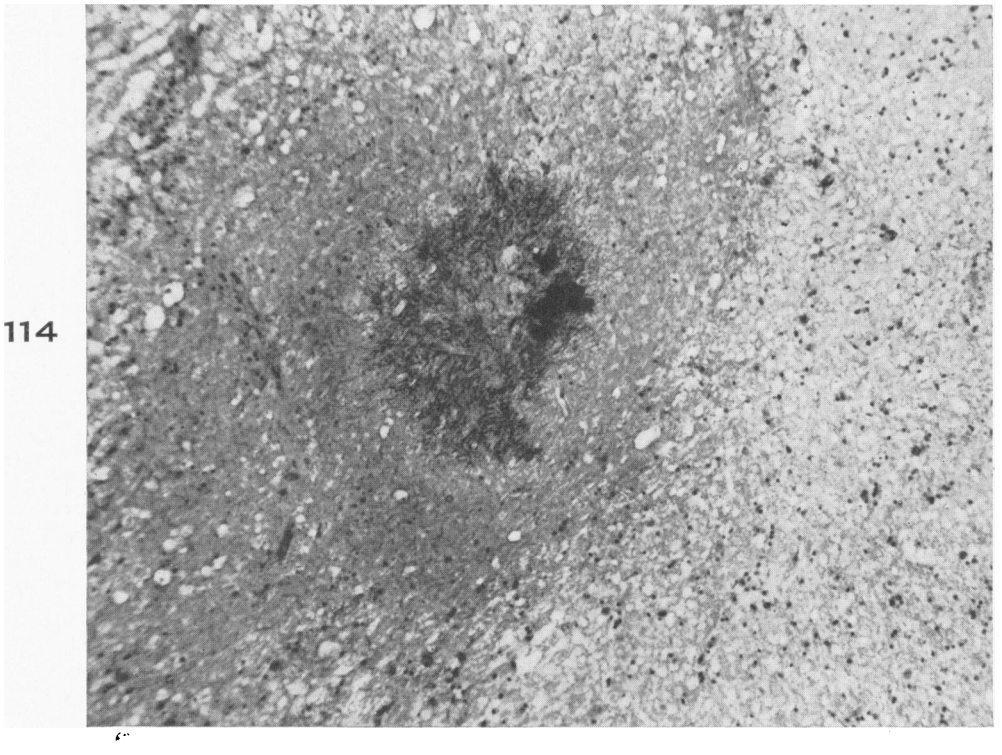


114

PLATE 157

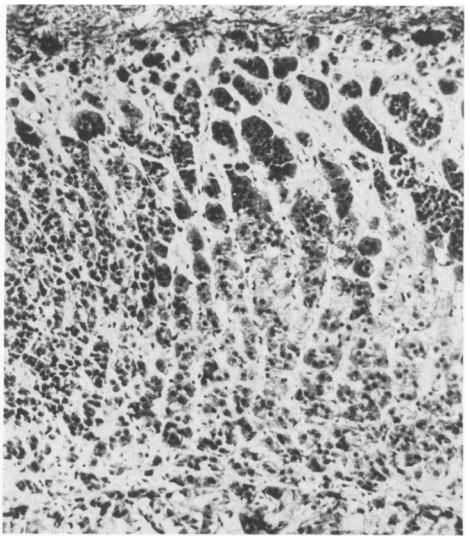
FIG. 115. Group III. Adrenal. Focal atrophy with decrease in thickness of cortex. Focal fatty changes in cortex. K-96. Sakoda. Male, 33 years of age. Approximately 1000 yds. Died on the 97th day. × 130.

FIG. 116. Group II. Atrophy of zona glomerulosa. Loss of lipid. Edema of subcapsular connective tissue. Masson's stain. K-2. Onishi. Male, 24 years of age. Approximately 800 yds. Died on the fourth day. A.I.P. neg. HM 124. × 60.

FIG. 117. Group II. Adrenal. Focus of necrosis in fascicular stratum of cortex. Infiltration of large fat-filled phagocytes. K-45. Akagi. Male, 28 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HM 236. × 265.

FIG. 118. Group II. Adrenal. Fatty changes of scattered cells and groups of cells in the cortex. Several epithelial cells in the fascicular stratum are in mitosis. From the same patient as Figure 117. A.I.P. neg. HM 237. × 210.

115



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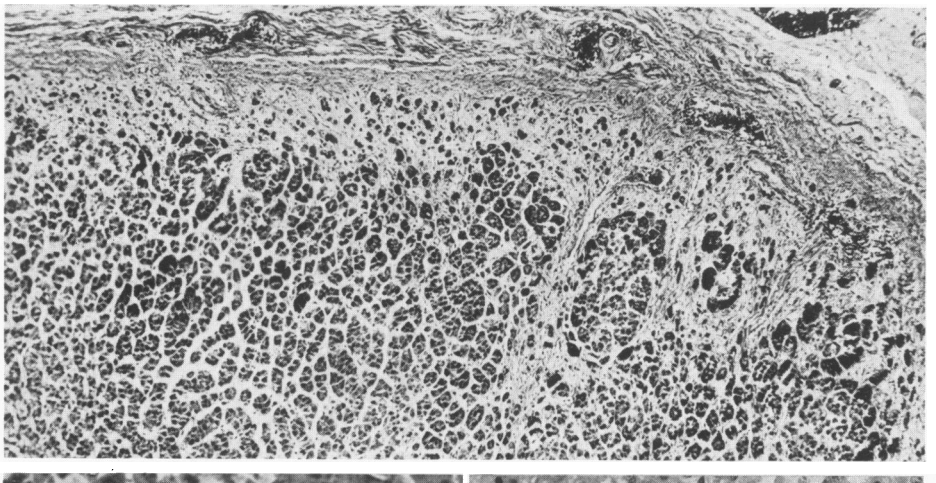

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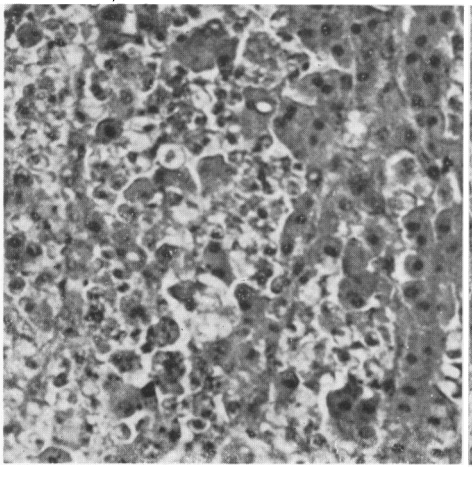
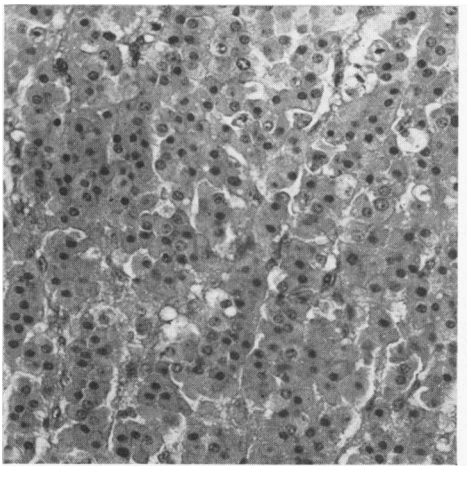




118

Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

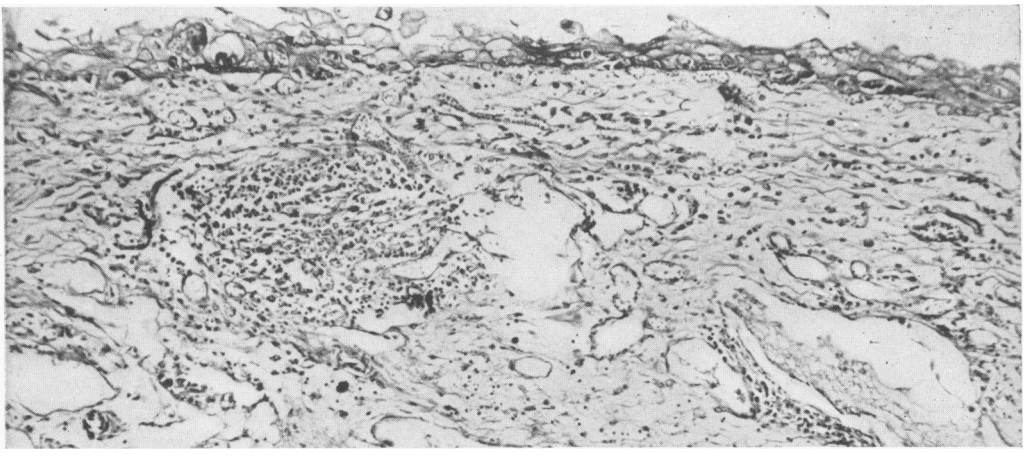
## PLATE 158

FIG. 119. Group I. Wall of pharynx. Swelling, vacuolation, fragmentation, and desquamation of the squamous epithelium. Edema of connective tissue. Atrophy of lymphoid tissue. Tremendous lymphectasia. Occasional plasma cells, mast cells, and large mononuclear elements scattered throughout the areolar tissue. K-98. Tamai. Male, 19 years of age. Distance unknown. Died on the tenth day. × 100.

FIG. 120. Group I. Pharynx. Epithelial swelling and fragmentation. Edema of deeper layers of wall. Enlargement of a portion of Figure 119. A.I.P. neg. HM 332. × 450.

FIG. 121. Group I. Swelling and vacuolation of some squamous epithelial cells. Atrophy of others. Swelling and loss of staining qualities of nuclei. Micronuclei (?) in one cell near surface. Parakeratosis at surface. Dilatation of lymphatics and edema of tongue. From the same patient as Figure 119. A.I.P. neg. HM 330a. × 130.

119



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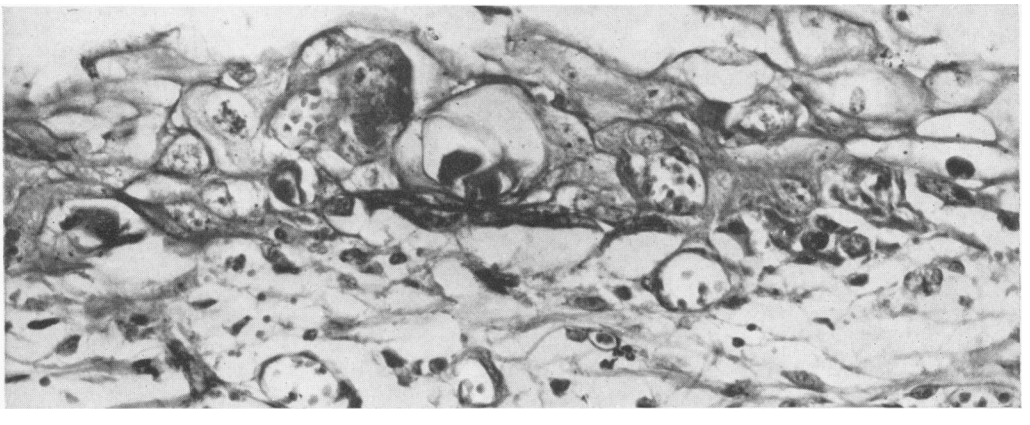

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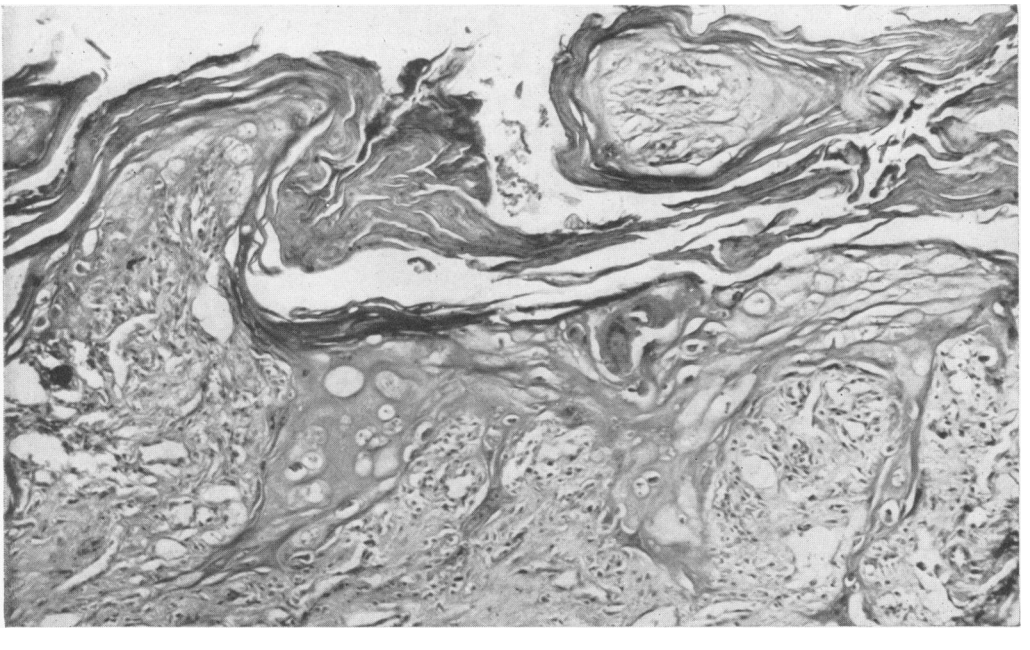


## PLATE 159

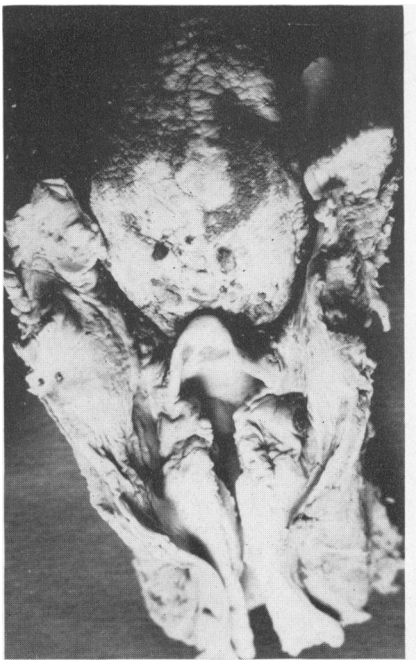
FIG. 122. Group II. Neck organs. Necrosis of lining membrane of epiglottis, larynx, and trachea. Necrosis and enlargement of left tonsil. Foci of necrosis in the right tonsil, which is somewhat smaller. K-21. Iseoka. Male, 45 years of age. Approximately 1000 yds. Died on the 24th day. A.I.P. neg. HS 300.

FIG. 123. Group II. Neck organs. Necrosis and hemorrhage of faucial and lingual tonsils, pyriform sinus, and epiglottis. K-44. Araki. Male, 22 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HS 328.

FIG. 124. Group II. Tongue. Necrosis and hemorrhage. K-29. Murakami. Male, 22 or 24 years of age (variously stated). Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HS 310.

FIG. 125. Group II. Tonsil. Necrosis. Absence of polymorphonuclear leukocytic barrier between the necrotic and non-necrotic tissue. K-47. Naka. Female, 35 years of age. Approximately 800 yds. Died on the 18th day. A.I.P. neg. HM 264. × 130.

122



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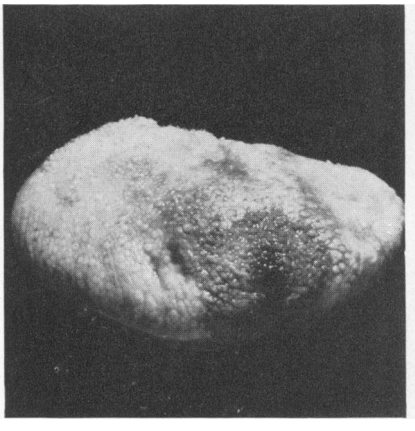

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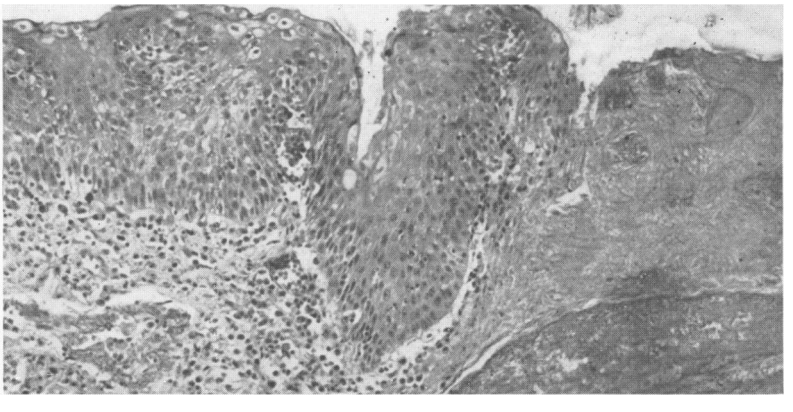


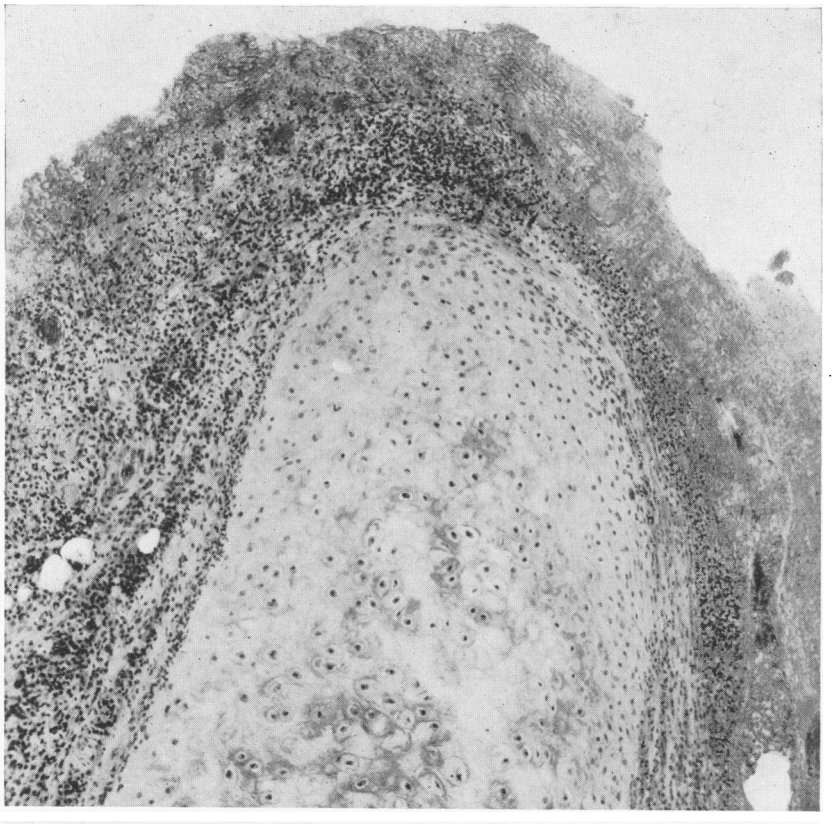
Liebow, Warren, and DeCoursey Pathology of Atomic Bomb Casualties

PLATE 160

FIG. 126. Group II. Epiglottis. Necrosis and infiltration of small mononuclear and plasma cells. Occasional polymorphonuclear leukocytes. Cartilage intact. K-56. Kawamura. Female, 51 years of age. Approximately 1100 yds. Died on the 36th day. A.I.P. neg. HM 270. × 115.

FIG. 127. Group II. Pharynx. Thrush. Mycelium (probably of monilia). From the same patient as Figure 126. A.I.P. neg. HM 271. × 130.

126



127

PLATE 161

FIG. 128. Group II. Patient with petechiae of skin. Epilation appeared on August 18, gingival hemorrhages and petechiae of skin began on August 29. Step-like rise of temperature began on August 31. Necrotizing tonsillitis was noted on September 1, delirium on September 2, and death occurred on September 3, 1945. Laboratory data on day of death: red blood cells, 2.03 millions; hemoglobin, 40 per cent; white blood cells, 1900; platelets, 10,400; bleeding time, 46 minutes. Hashimoto. Male, 21 years of age. Exact distance unknown. No record of autopsy. Photograph made by Japanese medical officers of Tokyo 1st Military Hospital 2 hours before the patient expired. A.I.P. neg. HP 135.

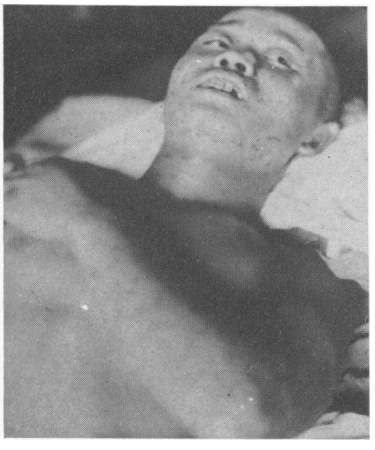
FIG. 129. Group II. Skin. Low-power view of margin of ulcer, and adjacent tissues. K-47. Naka. Female, 35 years of age. Approximately 800 yds. Died on the 18th day. A.I.P. neg. HM 344. × 30.

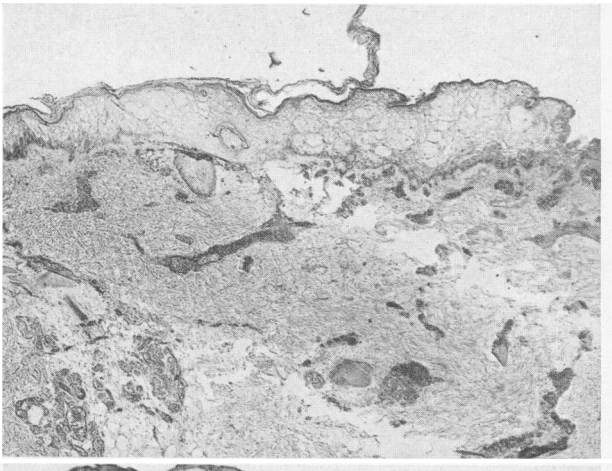
FIG. 130. Group II. Skin. Ulcer. Bacterial masses in necrotic material. Plasma cells, large mononuclear cells and extravasated erythrocytes at base. K-29. Murakami. Male, 24 or 22 years of age (variously stated). Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 296. × 115.

FIG. 131. Group II. Skin. Margin of ulcer. Necrosis of outer layers of epithelium. Pigment remains in basal cells. Congestion of blood vessels and hemorrhages. Bacteria in necrotic material at surface of ulcer. No leukocytic infiltration. Enlargement of a portion of Figure 129. A.I.P. neg. HM 299. × 115.

FIG. 132. Group II. Skin, at distance from ulcer. Vacuolation of epithelial cells and shrinkage of nuclei. Irregularity of distribution of pigment and absence of mitotic figures in basal layer. Small mononuclear cells about dilated blood vessels in corium. Enlargement of a portion of Figure 129. A.I.P. neg. HM 345. × 150.

128





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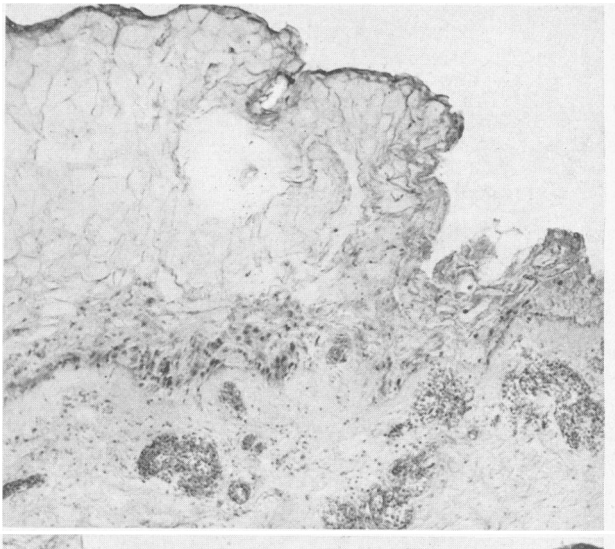

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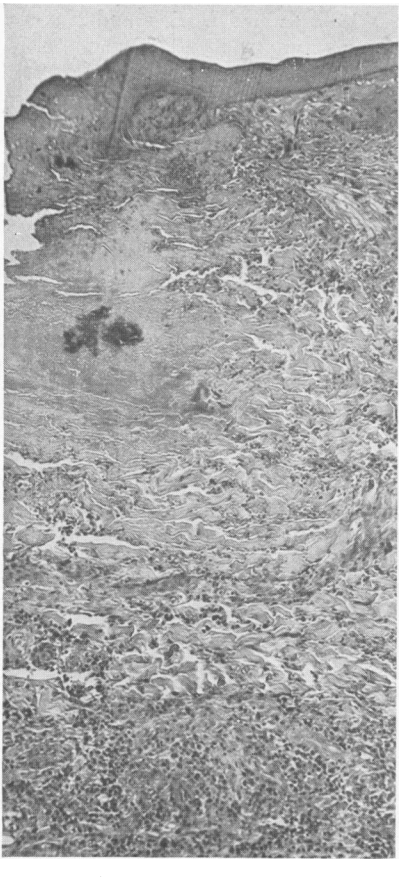
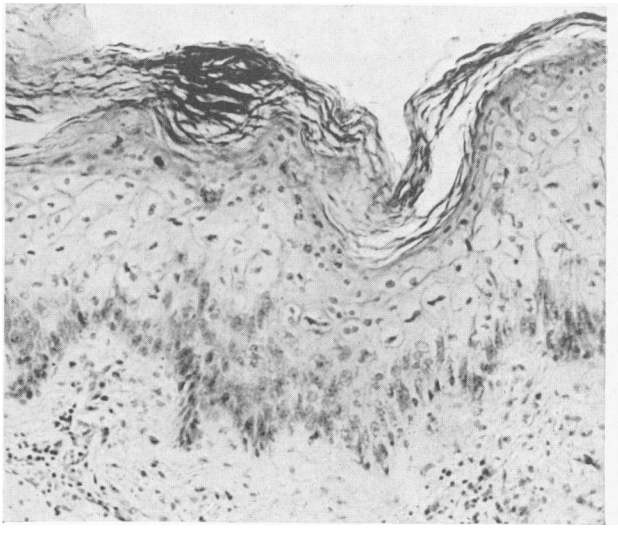




132

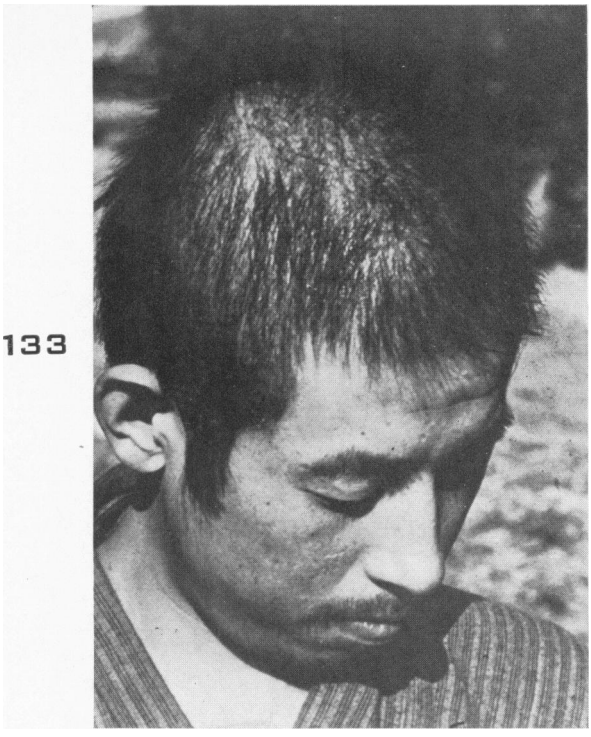
## PLATE 162

FIG. 133. Regrowth of hair, following epilation. Patient had been approximately 1000 yds. from the explosion on the upper floor of a two-story Japanese building in Hiroshima. Epilation began on August 20, 2 weeks after the bombing. His white blood cell count had fallen to as low as 900 on September 4 and he had had fever, petechiae, and ulcerative and hemorrhagic gingivitis from which he recovered. Approximately 2½ months after the bombing. A.I.P. neg. HP 125.

FIG. 134. Group III. Scalp. Regenerating hair follicle to illustrate typical structure. Occasional mitotic figures among matrix cells. Well defined Henle's and Huxley's layers and external root sheath. Cuticle is forming. K-14. Yamamoto. Male, 25 years of age. Approximately 1000 yds. Died on the 47th day. A.I.P. neg. HM 210. × 225.

FIG. 135. Group II. Scalp. Atrophy of hair follicle, thickening of glassy and basement membranes. Failure of differentiation of internal root sheath. Irregularity of distribution of pigment. Vacuoles between epithelium and glassy membrane. K-45. Akagi. Male, 38 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HM 238. × 130.

FIG. 136. Group II. Scalp. Hair follicle. Atrophy. Failure of differentiation of matrix. Irregularity of distribution of pigment. Tremendous thickening of glassy membrane. Remains of external root sheath have shrunken away from it. K-33. Ikeda. Male, 36 years of age. Approximately 1000 yds. Died on the 27th day. A.I.P. neg. HM 222. × 130.



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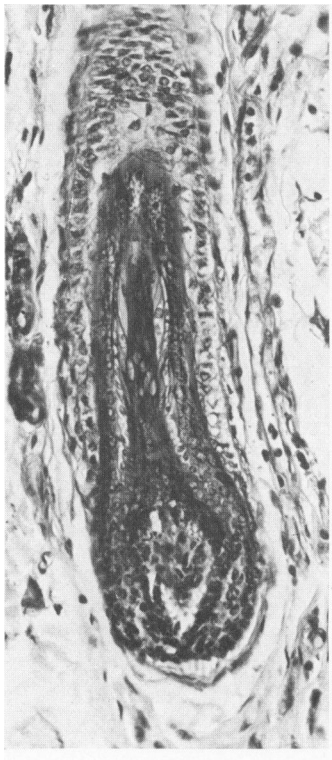

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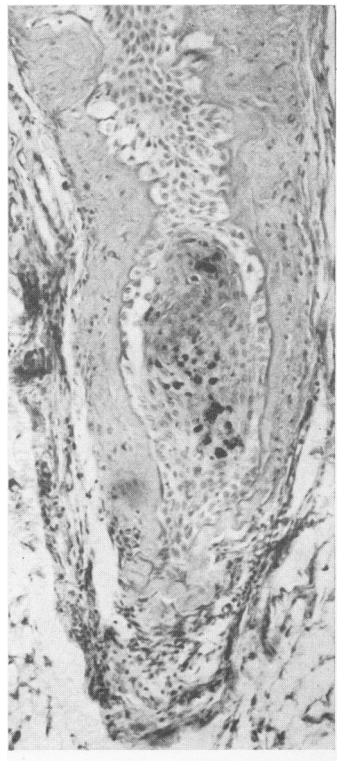


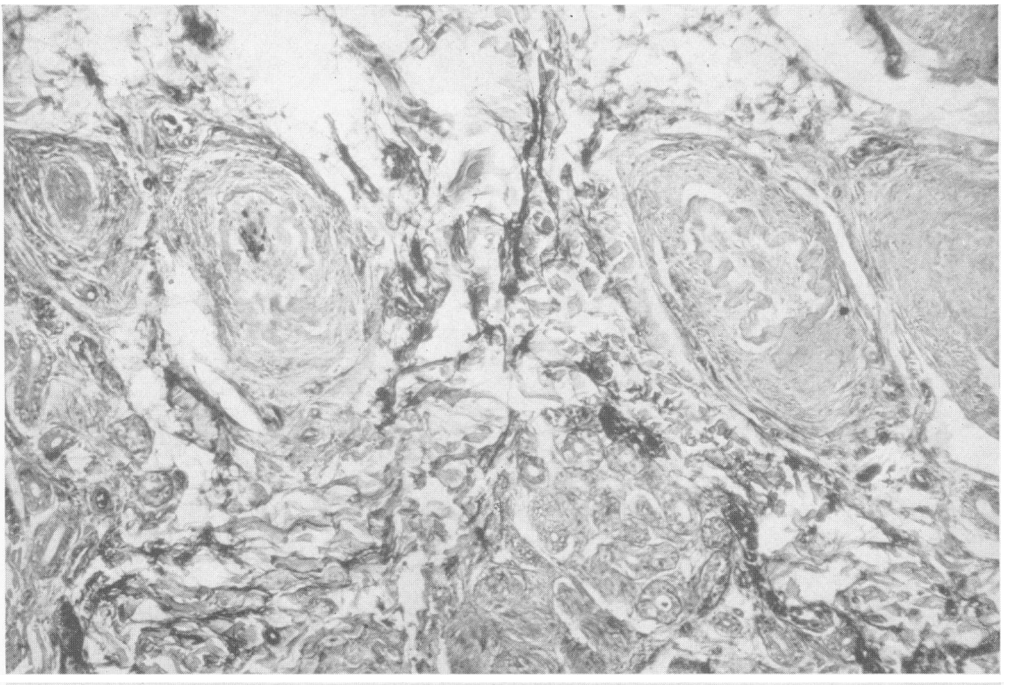
136

PLATE 163

FIG. 137. Group II. Scalp. Atrophy of hair follicles. Failure of differentiation of matrix substance. Irregular distribution of pigment. Enormous thickening of basement membrane and of glassy membrane which is proved not to be elastic tissue by Verhoeff's stain. The elastic fibers of the derma stain well. K-30. Nagashima. Male, 23 to 28 years of age (variously stated). Approximately 1000 yds. Died on the 26th day. A.I.P. neg. HM 215.

FIG. 138. Group II. Scalp. Atrophy of hair follicles. Enormous thickening of basement membranes. Atrophy of sebaceous glands. K-24. Chiba. Male, 29 years of age. Approximately 1000 yds. Died on the 25th day. A.I.P. neg. HM 294. × 20.

137



138

PLATE 164

FIG. 139. Group II. Scalp. Hair follicle. Atrophy. Hair remains fused to external root sheath. Process analogous to parakeratosis at surface. Irregularity of distribution of pigment. K-45. Akagi. Male, 28 years of age. Approximately 1000 yds. Died on the 33rd day. A.I.P. neg. HM 239. × 130.

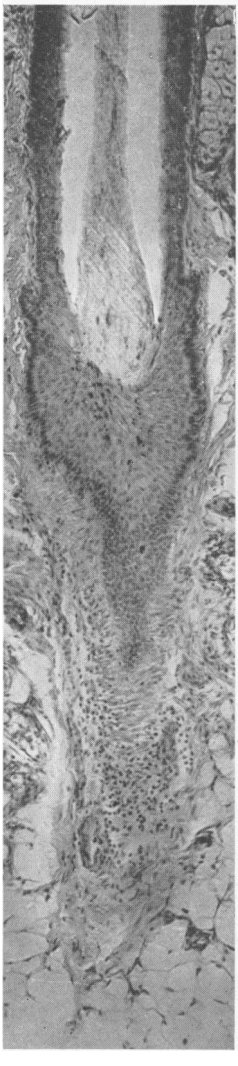
FIG. 140. Group II. Hair. removed from head of partly epilated person. Tapering of shaft toward attached end; evidence of atrophy of matrix. Absence of remnants of internal root sheath. K-35. Takahashi. Male, 31 years of age. Approximately 1000 yds. Died on the 28th day. A.I.P. neg. HM 262. × 50.

FIG. 141. Group III. Scalp. Hair. (See also Fig. 38.) The complete follicle in longitudinal section. Atrophy of matrix. Failure of differentiation of internal root sheath. Irregular distribution of pigment. Thickening of glassy and connective tissue sheath. Remnants of atrophic shaft fill the dilated mouth of the follicle. Parakeratotic plug around this shaft. Atrophy of associated sebaceous gland. Other follicles are in process of regeneration (Figs. 134 and 142). K-14. Yamamoto. Male, 25 years of age. Approximately 1000 yds. Died on the 47th day. A.I.P. neg. HM 238. × 50.

FIG. 142. Group III. Regeneration of a hair is beginning at the base of the follicle by a renewed differentiation of matrix cells (in close apposition to the connective tissue papilla) and of the internal root sheath. From the same patient as Figure 141. A.I.P. neg. HM 208. × 115.

FIG. 143. Normal cycle of loss and replacement of a hair. At the left an external and an internal root sheath are still differentiated. At *b* the latter is no longer visible, and the former has become shrunken. There is a thickening both of the glassy and external cellular basement membrane. At *c*, *d*, and *e* there are successive stages of that process and the old hair is being extruded. At *f* the internal root sheath is being differentiated anew, and at *g* the new hair is pushing outwards in the old follicle. From Pinkus.[68] A.I.P. neg. HM 307.

139



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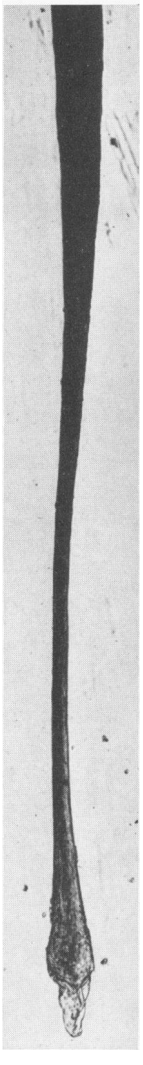

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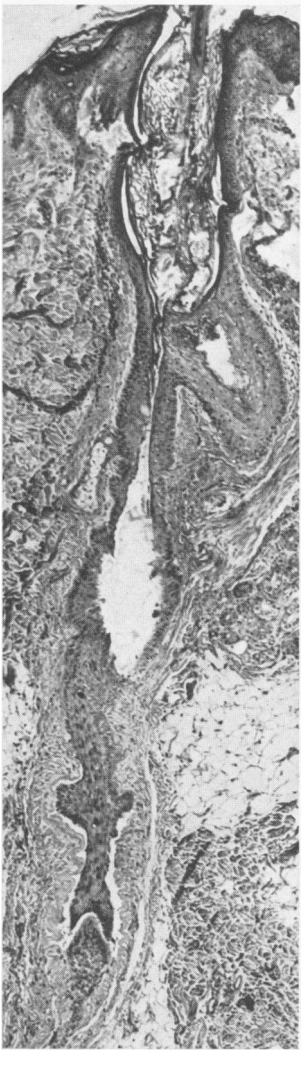

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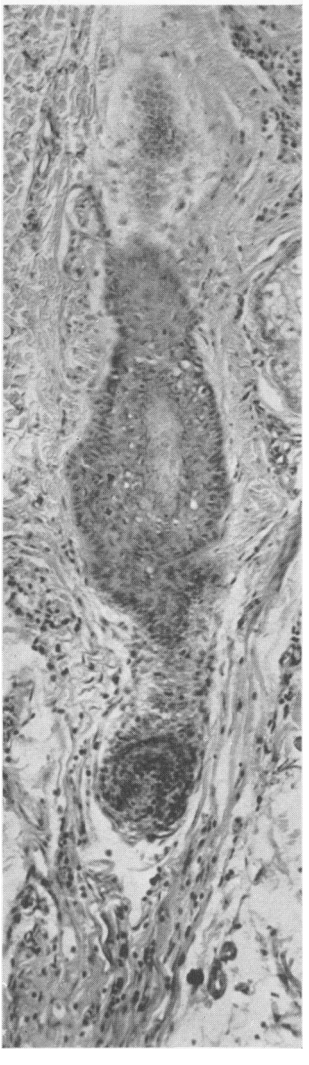

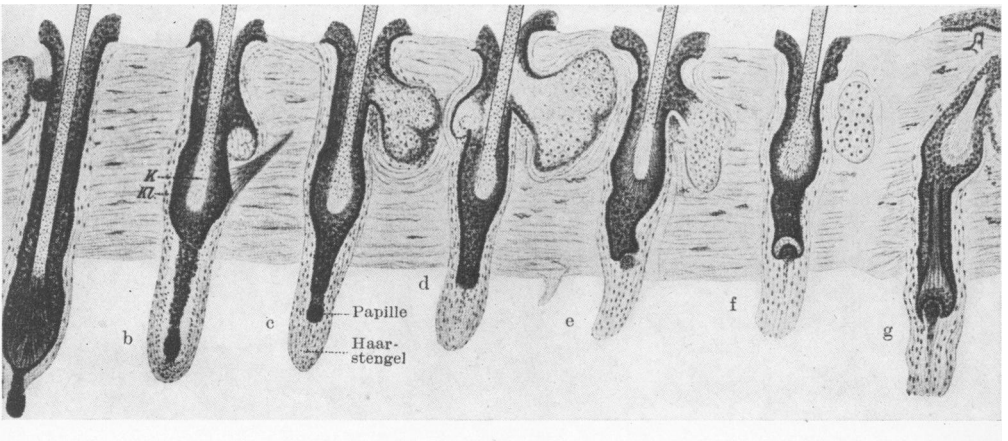


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